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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TABLE 1. Characteristics of Pyrazolo[3,4-d]pyrimidines II

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Chemical shifts, δ, ppm			^{79}Br NQR frequency, MHz	Yield, %
		C	H	Br	N		C	H	Br	N	C_6—H	starting I C_3—H	starting I C_6—H		
IIa	350	28,1	1,6	37,2	25,9	$C_5H_3N_4OBr$	27,9	1,4	37,2	26,1	9,40	9,12	9,49	301,62	90
IIb	310	31,4	2,3	35,2	24,7	$C_6H_5N_4OBr$	31,5	2,2	34,9	24,5	9,16	9,00	9,14	297,52	70
IIc	261—263			34,5	24,1	$C_6H_5N_4OBr$			34,9	24,5	9,58	9,09	9,61	292,93	80
IId	164—166	34,6	2,9	33,0	22,7	$C_7H_7N_4OBr$	34,6	2,9	32,9	23,1	9,32	9,04	9,25	289,55	80
IIe	233—234	34,6	2,8	32,9	22,8	$C_7H_7N_4OBr$	34,6	2,9	32,9	23,1	9,56	8,97	9,58	306,70	80

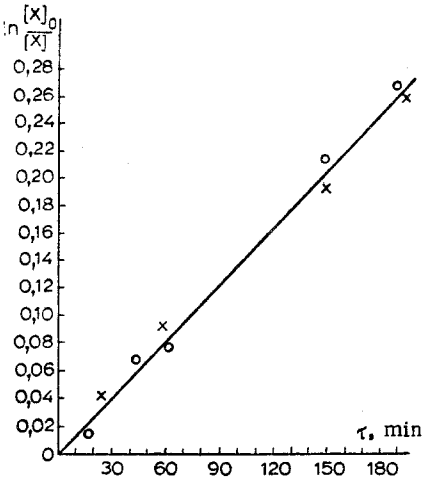

Fig. 1

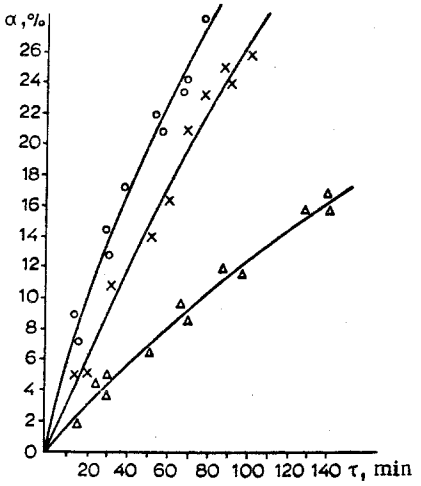

Fig. 2

Fig. 1. Dependence of the logarithm of the ratio of the starting bromine concentration on the reaction time for $[A]_0$ = $9.2 \cdot 10^{-3}$ M: ×) $[X]_0 = 1.60 \cdot 10^{-3}$ mole/liter; 0) $[X]_0 = 0.8 \cdot 10^{-3}$ mole/liter.

Fig. 2. Dependence of the degree of conversion of bromine [$\alpha = ([X]_0 - [X])/[X]_0$] on the reaction time for Ia and $[X]_0$ = $(1.5\text{-}1.6) \cdot 10^{-3}$ mole/liter: Δ) $[A]_0 = 9.2 \cdot 10^{-3}$ mole/liter; ×) $[A]_0 = 4.7 \cdot 10^{-3}$ mole/liter; 0) $[A]_0 = 2.7 \cdot 10^{-3}$ mole/liter.

The present paper is devoted to a detailed study of the bromination of I and its N-methyl derivatives.

The reaction was carried out by treatment of a suspension of I in water with bromine. Compounds Id,e underwent reaction at room temperature, whereas the remaining compounds were heated on a boiling-water bath. The reaction was complete after 1.5-2 h in all cases. Compounds IIa-e are stable compounds that are only slightly soluble in water and organic solvents.

I-II a R=R'=H; b R=H, I-R'=CH_3; c R=CH_3, R'=H; d R=I-R'=CH_3; e R=2-R'=CH_3

The structures of the products were confirmed by the results of elementary analysis and the PMR spectral data (Table 1). We have previously established that Ia-e molecules associate to give complexes in concentrated D_2SO_4 and particularly in deuterotrifluoroacetic acid and that there is an anomalous shift of all of the PMR signals to strong field [4]. A shift

of all of the signals to strong field is also observed in the PMR spectra of the bromo derivatives in concentrated trifluoroacetic acid, but we were unable to ascertain the principle behind this shift. Dilute D_2SO_4 was therefore used as the solvent. At H_0 values from 0 to −3 all of the starting Ia-e exist in the form of monocations and have virtually constant chemical shifts for the protons attached to the $C_{(3)}$ and $C_{(6)}$ atoms [4]. It is apparent from Table 1 that the introduction of bromine in the 3 position does not change the order of protonation. The signal of the proton attached to the $C_{(3)}$ atom vanishes in the spectra of all IIa-e; this constitutes evidence that electrophilic substitution occurs at the $C_{(3)}$ atom.

Nuclear quadrupole resonance (NQR) data serve as an additional confirmation of the presence of a bromine atom in the 3 position of these compounds. Thus the substantial difference in the ^{79}Br NQR frequencies in the spectra of dimethyl derivatives IId, and IIe, which is more than 17 MHz, indicates unambiguously that the bromine atom in these compounds is in the pyrazole ring. The absence of this considerable difference in the NQR frequencies for IIa and IIb attests to the presence of a hydrogen atom in the 1 position for pyrazolopyrimidine IIa in the solid state. This is in agreement with the existing ideas regarding the NQR frequencies of halogen in the α and β positions with respect to the "pyrrole" nitrogen atom [5]. The increase in the NQR frequency on passing from IId to IIb,c, in which the positions of the bromine atom relative to the "pyrrole" nitrogen atom are identical, should be explained by the effect of the intramolecular N—H...Br bonds; bonding of this type is excluded for IId,e.

In order to ascertain the effect of methyl substituents on the reactivities of I and to study the mechanism of the reaction we made a detailed investigation of the kinetics of the reaction of pyrazolopyrimidine Ia with bromine. It was established that the reaction is first-order with respect to bromine: The experimental points (Fig. 1) in coordinates of $\ln([X]_0/[X])$ and τ (where $[X]_0$ and [X] are the initial and instantaneous Br_2 concentrations, respectively, and τ is the reaction time) lie on a straight line, and the slope of the line is independent of $[X]_0$ for an identical initial concentrations of Ia, i.e., equation $v = k_{eff}[X]$ is valid. Unexpected results were obtained during a study of the dependence of the reaction rate on the initial concentration ($[A]_0$) of pyrazolopyrimidine Ia in the case of identical $[X]_0$ in solution. It follows from the data presented in Fig. 2 that as the initial Ia concentration decreases, the conversion of bromine (α) for the same period of time increases. This indicates inhibition of the reaction by the heterocycle; the degree of inhibition increases as the initial concentration of Ia is increased. It was assumed that the inhibition of the reaction by the starting compound is associated with complexing of the reacting substances. It is known that five- and six-membered heterocycles are capable of forming 1:1 complexes of the nσ type with halogens; these complexes may be formed prior to electrophilic substitution. In addition to 1:1 complexes, πσ complexes in a molar ratio of 2:1 may also be formed, in which case the bromine in the complexes is determined iodometrically as free bromine [8, 9].

The NQR and UV spectra were used to establish the possibility of complexing of pyrazolo-[3,4-d]pyrimidines with bromine. The NQR spectra of complexes of bromine with various n and π donors have been subjected to rather detailed study (for example, see [6]). 3-Bromopyrazolo[3,4-d]pyrimidine (IIa) was selected as the subject for the study, since the presence of a bromine atom in the donor system should have made it possible to observe not only πσ but also nσ complexes in the NQR spectra. When the donor molecule did not contain bromine, the formation of a complex could be judged only from the change in the NQR frequency of the Br_2 molecule, which in an nσ complex should go beyond the limits of the frequency range of the spectrometer used (up to 350 MHz). In the case of a π donor charge transfer to the acceptor usually decreases the population of the p_x orbital of the bromine atom in the aromatic system and, consequently, its NQR frequency; this was observed in the case of the IIa molecule. As seen from Table 3, the shift of the ^{79}Br NQR signal to the low-frequency region is 1.57%. An increase in the population of the p_z orbital of the halogen atom and a corresponding decrease in the NQR frequency should be observed for the simplest σ acceptors (Br_2, I_2, ICl, etc.) during the formation of a πσ complex if charge transfer to the p orbital is realized; however, there are also exceptions. For example, slight high-frequency shifts due to the determining role of the steric interactions are observed in the ^{81}Br NQR spectra of the $Br_2 \cdot C_6H_6$ and $Br_2 \cdot O(C_2H_5)_2$ complexes. The small high-frequency shift (0.9%) for Br_2 in the $Br_2 \cdot$IIa complex can probably be ascribed to the same exceptions (see Table 3). In the spectrum of the investigated complex the frequencies of both atoms of the bromine molecule coincide, which

TABLE 2. Experimental Values of the Degree of Conversion of Bromine

Compound I	a	b	c	d	e
$[A]_0$, mole/liter 10^{-3}	2,55; 9,2	3,00; 6,3	3,03; 8,00	4,6; 9,75	3,00; 9,00
$[X]_0$, mole/liter 10^{-3}	1,55; 1,60	1,60; 1,65	1,65; 1,60	1,60; 1,60	1,55; 1,60
α, %	17,5; 6,5	9,5; 5,0	20,0; 23,0	18,0; 21,0	12,5; 16,0

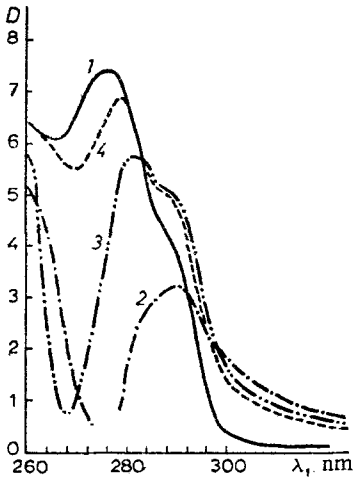

Fig. 3. UV Spectra of CCl_4 solutions of: 1) the starting mixture of Id with bromine (c_{Id} $1.45 \cdot 10^{-4}$ mole/liter, c_{Br_2}/c_{Id} 2:1, 1:1, and 1:2), 2) the 2:1 mixture after 48 h; 3) the 1:1 mixture after 48 h; 4) the 1:2 mixture after 48 h.

means that they are chemically and crystallographically equivalent. It may be assumed that this complex is a $\pi\sigma$ complex and, like complexes of bromine with benzene, acetone, and dioxane [6], has a chain structure.

The ability of pyrazolo[3,4-d]pyrimidines to undergo complexing with bromine was confirmed by the UV spectral data. A rapidly vanishing increase in the optical density with a small bathochromic shift relative to the absorption maximum of the starting heterocycle is observed under the conditions of the kinetic experiments for Ia. The appearance of this maximum can be explained by the formation of a charge-transfer complex (CTC) (Fig. 3). However, acetic acid, in which the spectra were obtained, has the disadvantage that it has a specific interaction with the halogen and the heterocycle. We therefore selected another solvent — CCl_4, which does not have these properties; we recorded the spectrum of pyrazolopyrimidine Id, which is the only compound of the investigated series that is soluble in CCl_4. It follows from Fig. 3 that the spectra of 1:2, 1:1, and 2:1 mixtures of Id with Br_2 coincide. After 48 h at 20°C considerable changes are observed in the spectra of the mixture of I: The maximum of compound Id vanishes, and a new band, which is shifted bathochromically relative to the starting compound and brominated product and can be assigned to a charge-transfer complex with a sufficient degree of likelihood, appears. With respect to the form of the curve, this spectrum is characteristic for complexes of halogens with heterocycles — it has more sloping character in the long-wave region, which usually constitutes evidence of the presence in the system of complexes of the $n\sigma$ and $\pi\sigma$ types [10]. The decrease in the absorption intensity is explained by precipitation of the reaction product from the mixture. Smaller changes in the spectrum for the same period of time because of a decrease in the reaction rate are observed for equal and excess concentrations of Id relative to bromine.

We attempted to explain the unusual fact of inhibition of the bromination reaction on the basis of the literature and experimental data. It was assumed that Ia (A) may form two complexes — a 1:1 complex and a 2:1 complex — with bromine under the selected conditions.

$$A + X \underset{}{\overset{K_1}{\rightleftharpoons}} AX \xrightarrow{k} \text{Product} + Br^-;$$

$$2A + X \overset{K_2}{\rightleftharpoons} A_2X. \qquad (1)$$

TABLE 3. NQR Frequencies of IIa and Its Complex with Br_2 at 77°K

Compound	ν ^{79}Br, MHz	ν ^{81}Br, MHz
IIa	301.62	
Br_2		319.57
Br_2+IIa	296.88	322.50
	293.15 (very weak signal)	

The rate-determining step of the reaction is evidently decomposition of the AX complex to give the product, so that the reaction rate is determined by the equation

$$v = k[AX]. \tag{2}$$

In agreement with the law of mass action for equilibria the ratio of the concentrations of these complexes is described by the equation

$$[AX]/[A_2X] = K_1/K_2 \cdot 1/[A]. \tag{3}$$

We will assume that in the case of an excess amount of A relative to the halogen virtually all of the titrated bromine enters into the composition of the complexes, making the following equation valid:

$$[X] = [AX] + [A_2X]. \tag{4}$$

Hence the reaction rate can be expressed by Eq. (5), which reflects the dependence of the rate of bromination on the concentrations of pyrazolopyrimidine I and bromine that are experimentally observed – the reaction is first-order with respect to bromine and is inhibited by the heterocycle:

$$v = \frac{[X]K_1/K_2}{K_1/K_2 + [A]}. \tag{5}$$

In conformity with the experimental data, the degree of inhibition according to Eq. (5) increases as the initial concentration of the heterocycle increases. In addition to pyrazolopyrimidine Ia, the inhibition effect is observed only for Ib. The unreactive complex evidently has low stability in the case of $N_{(5)}$-substituted pyrazolo[3,4-d]pyrimidine, and its formation has virtually no effect on the reaction rate. In addition, as seen from Table 2, the reaction rate remains virtually unchanged as the concentration of the heterocycle is increased; this is usually observed for reactions that proceed with the formation of an intermediate when its maximum concentration is reached. The certain decrease in the rate of bromination when a methyl group is introduced in the 1 position of the pyrazole ring is difficult to explain unambiguously on the basis of the available data. It is possible that this is associated with the lower stability of the reactive intermediate complex.

The combination of methods used in this research confirms the assumption that bromination proceeds through the formation of a reactive complex. A nonreactive complex containing twice as much and possibly more heterocycle than halogen is formed simultaneously.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in 12 N D_2SO_4 were obtained with a Varian Ha/100 spectrometer with hexamethyldisiloxane as the external standard; the accuracy in the measurements was ± 0.01 ppm. The UV spectra of the compounds were recorded with a Shimadzu MPS-50L spectrophotometer in 1-cm cuvettes at 27°C. The NQR spectra were recorded at 77°K with an ISSh 1-13 spectrometer manufactured by the Special Design Office of the Institute of Radio Engineering and Electronics of the Academy of Sciences of the USSR.

The kinetic studies in 50% acetic acid were made at 45 ± 1°C.

Sodium bromide (0.1 mole/liter) was added to maintain a constant ionic strength. An excess amount of the heterocycle with respect to bromine (2-12:1) was used in all of the experiments; the bromine concentration was $(1.5\text{-}1.7)\cdot10^{-3}$ mole/liter. The bromination products were identified by means of thin-layer chromatography (TLC). The bromine content of samples selected at definite time intervals was determined by iodometric titration; the decrease in the bromine concentration was judged from the rate of the process. The measurements were made at a low degree of conversion, and the data obtained therefore correspond to the initial reaction rates that are far from the equilibrium values.

The reagents were prepared by the method in [8]. Chromatography was carried out on Silufol UV-254 plates with the following systems: 1) ethyl acetate—methanol—chloroform (6:1:2); 2) methanol—chloroform (2:1).

In the recording of the NQR spectra the heterocycle was dissolved in bromine, the solution was allowed to stand for 24 h, the excess bromine was removed, and the spectrum was recorded.

3-Bromo-4-hydroxypyrazolo[3,4-d]pyrimidine (IIa). A 1.36-g (0.01 mole) of Ia was suspended in 25 ml of water, 1.5 g of bromine was added, and the mixture was stirred at room temperature for 1 h and heated on a boiling-water bath for 1.5 h. It was then cooled, and the precipitate was suspended in 50 ml of hot water. The suspension was treated with 2 N NaOH to dissolve the solid, and the solution was acidified with acetic acid to pH 6-7 and worked up to give IIa. Compound IIb was similarly obtained. Compounds IIc-e were obtained by the same method with exclusion of heating on a water bath and reprecipitation from alkali by the addition of acetic acid.

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