crystals, with mp 157-158°C (from hexane), in 5% yield. IR spectrum: 1630 (C=O); 1380 and 1540 cm^{-1} (NO_2). Found: C 55.2; H 4.2; N 13.6%. $C_{14}H_{13}N_3O_5$. Calculated: C 55.4; H 4.3; N 13.8%. Compounds IIa, b were oxidized by the method in [8].

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PYRIMIDINES

LXVI.* BROMINATION OF SUBSTITUTED 4-PHENYLPYRIMIDINE 1-OXIDES

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It is shown that the bromination of 4-phenylpyrimidine 1-oxide takes place in the 5 position of the pyrimidine ring. When there is a methyl group in the pyrimidine N-oxide molecule, it also undergoes bromination. The direction of the reaction depends on the bromination conditions. A bromine atom in the 5 position of pyrimidine N-oxide is readily exchanged by a methoxy group.

The chemical properties of azines are changed substantially when an N-oxide group, which is capable of displaying both acceptor and donor properties [2], is introduced. Of the N-oxides of azines, little study has been devoted to pyrimidine derivatives [2], although a number of papers involving the study of the chemical properties of pyrimidine N-oxides have recently appeared [3-6]. Continuing our research on pyrimidine derivatives [1] we became interested in the possibility of using pyrimidine N-oxides for the synthesis of some difficult-to-obtain compounds, particularly alkyl- and aryl-substituted 5-halopyrimidines [7, 8]. No information on the halogenation of pyrimidine N-oxides is available in the literature. We studied the reactions of some pyrimidine N-oxides with brominating agents such as bromine and N-bromosuccinimide (NBS), taking into account the fact that the bromine-containing compounds are the most interesting of the halo derivatives because of the high lability of the bromine atom.

We used 4-phenylpyrimidine 1-oxide (Ia) and 6-methyl- (Ib) and 2-methyl-4-phenylpyrimidine 1-oxide (Ic), which we obtained in 40-80% yields by oxidation of the corresponding pyrimidines with hydrogen peroxide in the presence of sodium tungstate in analogy with [9], as the starting compounds. We were unable to obtain 2,4-diphenylpyrimidine 1-oxide by this method or by oxidation of 2,4-diphenylpyrimidine with hydrogen peroxide in acetic acid. The difficulty involved in the oxidation of 2-phenylpyrimidines to N-oxides has already been previously noted [10], and compounds of this type have not yet been obtained. On the basis of the literature data on steric hindrance in the oxidation of the nitrogen atom of a heteroring adjacent to a phenyl group and the easier oxidation of a nitrogen atom

*See [1] for communication LXV.

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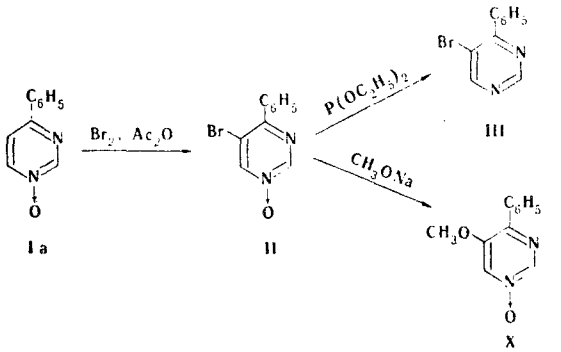
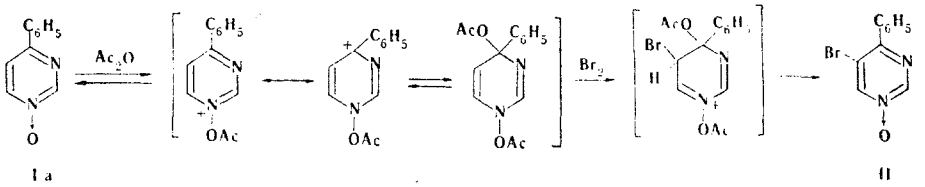
in the vicinity of alkyl substituents [11, 12], we assigned the position of the N-oxide group in the previously undescribed Ic. The correctness of structure Ic is confirmed by the coincidence of the absorption maxima in the UV spectra of Ia and Ic and the difference between the chromophore system of the latter and the 6-phenylpyrimidine 1-oxide system [5].

The bromination of Ia-c was carried out in analogy with the bromination of pyridine N-oxides [13]. When Ia was treated with a solution of bromine (in $CHCl_3$, CH_2Cl_2, and $C_6H_5NO_2$ at a reagent ratio of 1:1), no changes in the reaction mixture were observed visually and chromatographically even at elevated temperatures after 1 h, whereas the bromine color vanished very rapidly (20 min) when an equimolar amount of acetic anhydride was added to the reaction mixture. A bromine-containing compound was isolated from the complex reaction mixture; the highest yield of this product was obtained in acetic acid, and in this case the reaction also took place when acetic anhydride was absent, although the reaction time increased several times. The IR spectrum of this compound contains an intense absorption band at 1280 cm^{-1}, which is characteristic for the N→O group [14]. In addition to the signal of aromatic ring protons (7.42-7.86 ppm, 5H), the PMR spectrum (Table 1) contains signals at 8.97 ppm (1H, H^2) and 8.67 ppm (1H, H^6) and doublets with J = 2 Hz; this is characteristic for the splitting of protons separated by an N-oxide group [5, 15]. These spectral data are in agreement with the expected 5-bromo-4-phenylpyrimidine 1-oxide structure (II). To confirm the structure we reduced oxide II with triethyl phosphite to the known 5-bromo-4-phenylpyrimidine (III) [8].



In analogy with the data on the reaction of pyridine N-oxides in the presence of acetic anhydride [13], it may be assumed that the bromination of pyrimidine N-oxides proceeds via the scheme



N-Bromosuccinimide (NBS) can also be successfully used in place of bromine for the bromination of Ia in the 5 position of the pyrimidine ring.

The bromination of pyrimidines Ib and Ic with an equimolar amount of bromine proceeded less unambiguously than in the case of Ia. Thus four bromine-containing compounds, which were, according to the analytical data, two monobromo (IV and V) and two dibromo (VI and VII) derivatives of pyrimidine N-oxides ($\nu_{N\rightarrow O}$ 1250-1280 cm^{-1} in the IR spectra of all of the compounds), were isolated in the bromination of Ib. The PMR spectral data for these compounds make it possible to unambiguously establish the presence of an H^5 proton in oxides V (8.09 ppm) and VII (8.26 ppm) and its absence in VI and IV, as well as the presence of a CH_3 group in IV, a CH_2Br group in V and VI, and a $CHBr_2$ group in VII (Table 1). 5-Bromo-6-methyl-4-phenylpyrimidine 1-oxide (IV), 6-bromomethyl-4-phenylpyrimidine 1-oxide (V), 5-bromo-6-bromomethyl-4-phenylpyrimidine 1-oxide (VI), and 6-dibromomethyl-4-phenylpyrimidine 1-oxide (VII) structures were assigned to the compounds obtained on the basis of these data.

It is apparent from the UV absorption spectra of these compounds that the introduction of a bromine atom in the 5 position of the pyrimidine ring (compare Ia and II, Ib and IV, and V and VI) gives rise to a 10-15 nm hypsochromic shift of the absorption maximum at 300 nm (Table 2).

TABLE 1. PMR Spectra of Substituted Pyrimidine N-Oxides (δ, ppm, J in hertz)

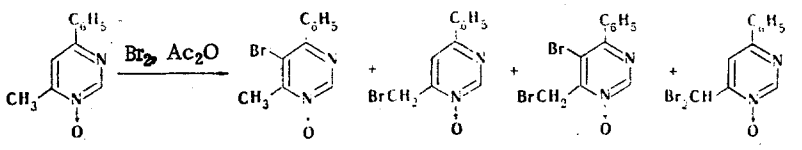
Compound*	H^2	H^5	H^6	CH_3 (or CH_2Br or $CHBr_2$)	CH_{arom} ($2H_o$ and $2H_m$ + H_n)
Ic	—	7,47 ($J_{5,6}$=7)	8,37 ($J_{5,6}$=7)	2,73 (CH_3)	7,95; 7,40
II	8,97 ($J_{2,6}$=2)	—	8,67 ($J_{2,6}$=2)	—	7,86—7,45
IV	9,08	—	—	2,79 (CH_3)	7,83—7,42
V	8,74	8,09	—	4,80 (CH_2Br)	8,12; 7,73
VI	9,11	—	—	4,86 (CH_2Br)	8,02; 7,40
VII	8,93	8,26	—	7,19 ($CHBr_2$)	8,00; 7,53
VIII	—	7,80 ($J_{5,6}$=7)	8,51 ($J_{5,6}$=7)	4,46 (CH_2Br)	7,80; 7,31
IX	—	7,73 ($J_{5,6}$=7,5)	8,49 ($J_{5,6}$=7,5)	6,93 ($CHBr_2$)	7,84; 7,24
X	8,73 ($J_{2,6}$=2)	—	8,27 ($J_{2,6}$=2)	3,75 (CH_3O)	7,82; 7,17

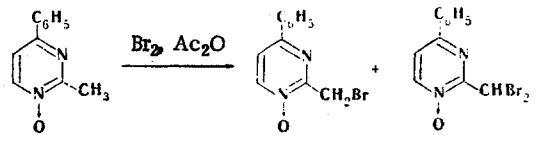
*The solvents used were d_6-DMSO for V, CF_3COOH for IX and X, and $CDCl_3$ for the remaining compounds.

TABLE 2. Substituted 4-Phenylpyrimidine 1-Oxides

Compound	mp, °C*	Found, %				Empirical formula	Calc., %				UV spectra, λ_{max}, nm (log ε)	Yield, %
		C	H	Br	N		C	H	Br	N		
Ic	154—155	70,6	5,6	—	14,9	$C_{11}H_{10}N_2O$	70,9	5,4	—	15,0	211 (4,25), 294 (4,16), 331 (4,23)	60
II	211—213	48,1	2,9	31,5	11,0	$C_{10}H_7BrN_2O$	47,9	2,8	31,9	11,1	210 (4,05), 229 (4,03), 296 (4,23), 326 sh (4,04)	40
IV	120—121	49,2	3,5	29,7	10,6	$C_{11}H_9BrN_2O$	49,9	3,4	30,1	10,6	208 (4,07), 229 (4,13), 294 (4,16)	17
V	188—191	50,5	3,6	29,8	10,8	$C_{11}H_9BrN_2O$	49,9	3,4	30,1	10,6	217 (4,18), 305 (4,27), 341 sh (4,00)	8
VI	157—158	37,6	2,5	—	8,1	$C_{11}H_8Br_2N_2O$	38,4	2,3	—	8,1	223 (4,10), 242 (4,09), 298 (4,20), 346 (3,72)	6
VII	139—141	38,8	2,5	45,7	8,1	$C_{11}H_8Br_2N_2O$	38,4	2,3	46,4	8,1	207 (4,05), 220 (4,12), 308 (4,27)	3
VIII	142—146	51,2	3,5	—	10,6	$C_{11}H_9BrN_2O$	49,9	3,4	30,1	10,6	207 (4,06), 220 (4,13), 311 (4,28)	16
IX	147—149	38,1	2,3	45,5	7,8	$C_{11}H_8Br_2N_2O$	38,4	2,3	46,4	8,1	207 (4,17), 220 (4,23), 313 (4,35)	24

*The compounds were recrystallized from alcohol (II, V, and VII), isopropyl ether (IV and VI), and isopropyl ether—isopropyl alcohol (Ic, VIII, and IX).





The ratio of reaction products IV-VII depends markedly on the bromination conditions — when the reaction is carried out in acetic acid at 80°C, the primary product is oxide VII, whereas mainly 5-bromo-derivative IV is obtained at 0°C.

In the case of Ic, in which the methyl group under the influence of the ring nitrogen atom and N-oxide group is more acidic than in pyrimidine Ib, 5-bromo derivatives of pyrimidine could not be detected in the bromination products, despite changes in the reaction conditions. In this case we isolated compounds with 2-bromomethyl- and 2-dibromomethyl-4-

phenylpyrimidine 1-oxide structures (VIII and IX), according to the PMR spectral data (Table 1).

Considering the predominant bromination of the methyl group in Ib and Ic, we subjected 5-methyl-4-phenylpyrimidine 1-oxide (Id) to this reaction. However, we were unable to detact bromomethyl derivatives of the N-oxide in the reaction mixture. The introduction of an activating N-oxide group evidently did not lead to a significant increase in the reactivity of the CH_3 group in the β position relative to the heteroatom of the pyrimidine ring. It is known that the rate of substitution of the chlorine atom in β-chloropyridine N-oxides increases by several orders of magnitude as compared with β-chloropyridines [16]. We verified the effect of an N-oxide group on the lability of the bromine atom in the pyrimidine derivatives by comparison of the behavior of II and III under the influence of sodium methoxide. Pyrimidine III does not undergo any changes when it is heated with sodium methoxide for 6 h, whereas oxide II undergoes complete reaction in 4 h; 5-methoxy-4-phenylpyrimidine 1-oxide (X) was isolated from the latter reaction mixture in good yield. Thus the halogen atom in the β position relative to the N-oxide group in the pyrimidine derivatives is considerably more labile than in unoxidized compounds, and this may be of great value for the synthesis of some difficult-to-obtain 5-methoxy derivatives of pyrimidine [17].

EXPERIMENTAL

The IR spectra of KBr pellets or solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A56/60 spectrometer with hexamethyldisiloxane as the internal standard; the chemical shifts are presented on the δ scale in parts per million. The individuality of the compounds was verified by means of thin-layer chromatography (TLC) on Silufol UV-254.

Oxidation of Ia-c with Hydrogen Peroxide and Na_2WO_4. Oxidation was carried out in analogy with [9]. After complete decomposition of the hydrogen peroxide, the residue was extracted with chloroform, and the extract was washed with 20% potassium carbonate solution and dried with magnesium sulfate. The solvent was removed by evaporation, and the residue was recrystallized from isopropyl ether–isopropyl alcohol (5:1) (see Table 2 for data on Ic) to give Id with 147-149°C (mp 151-153°C [18]). In the synthesis of Ia, cooling of the 30% hydrogen peroxide solution precipitated Ia, which was removed by filtration to give a product with mp 131-133°C (mp 132-134°C [5]) in 70% yield.

5-Bromo-4-phenylpyrimidine 1-Oxide (II). A) A 1.0-g (12 mmole) sample of sodium acetate and 2 ml of acetic anhydride were added to a solution of 0.8 g (4.6 mmole) of Ia in 20 ml of acetic acid, and the mixture was heated to 80°C and treated with a solution of 1.5 g (9.6 mmole) of bromine in 5 ml of acetic acid. The mixture was then stirred at this temperature until the bromine color vanished (1-2 h). The solvent was removed by vacuum distillation, and the residue was dissolved in chloroform. The solution was washed with water and evaporated, and the residue was triturated with 10 ml of acetone. The precipitated oxide II was removed by filtration (see Table 2).

B) A 1.1-g (6.2 mmole) sample of NBS was added to a refluxing solution of 0.6 g (3.4 mmole) of Ia and 0.8-ml (8.4 mmole) of acetic anhydride in 10 ml of chloroform, and the mixture was refluxed until starting oxide Ia vanished. The solution was evaporated, and the residue was triturated with 30 ml of hot water. The residual oil was triturated with ethyl acetate, and the precipitated II was removed by filtration to give 0.25 g (30%) of II with mp 210-213°C.

5-Bromo-4-phenylpyrimidine (III). A 0.5-g (2.0 mmole) sample of II was refluxed in 4 ml of triethyl phosphite for 30 min, after which the triethyl phosphite was removed by vacuum distillation, and the residue was recrystallized from petroleum ether (70-100°C) to give 0.3 g (60%) of III with mp 93-95°C (mp 95-97°C [8]).

Bromination of Ib. A solution of an equimolar (with respect to the oxide) amount of bromine in methylene chloride was added at 0°C to a mixture of oxide Ib, acetic anhydride, and sodium acetate in a ratio of 1:3:2.5 in methylene chloride, and the mixture was stirred at this temperature until the bromine color vanished. The inorganic salts were removed by filtration, the filtrate was evaporated, and the residue was extracted with acetone. The undissolved substance was removed by filtration to give V.

The acetone solution was evaporated, and the residue was separated with a column filled with silica gel (elution with ethyl acetate) to give successively, VII, VI, IV, and starting oxide Ib. The yields and analytical data for the compounds obtained are presented in Table 2.

The yields were as follows when the reaction was carried out at room temperature: 7% IV, 22% V, 6% VI, and traces of VII. Traces of IV, V, and VII and 27% VI were obtained in the case of Ib:Br_2 ratio of 1.0:1.5. Traces of IV, V, and VI and 45% VII were obtained when the reaction was carried out in acetic acid at 80°C.

Bromination of Oxide Ic. A solution of 0.5 g (3.0 mmole) of bromine in 2 ml of CH_2Cl_2 was added at 50°C to a mixture of 0.6 g (3.0 mmole) of Ic, 0.9 ml (9.5 mmole) of acetic anhydride, and 0.6 g (7 mmole) of sodium acetate in 12 ml of methylene chloride, and the mixture was stirred for 20 min. The inorganic salts were removed by filtration, the filtrate was evaporated, and the residue was separated with a column filled with silica gel by means of successive elution with CCl_4, EtOAc, and MeOH (and mixtures of them) to give VIII and IX (see Table 2).

5-Methoxy-4-phenylpyrimidine 1-Oxide (X). A 0.5-g (2.0 mmole) sample of oxide II was refluxed in a solution of 3.9 mmole of sodium methoxide in 25 ml of absolute methanol for 4 h, after which it was neutralized with acetic acid and filtered. The filtrate was then evaporated, and the residue was washed with water to give 0.25 g (60%) of X with mp 173-176°C (from isopropyl ether–isopropyl alcohol). UV spectrum (in alcohol), λ_{max} (log ε): 207 (4.23), 226 (4.18), and 344 nm (4.37). Found: C 65.3; H 5.2; N 14.3%. $C_{11}N_{10}N_2O_2$. Calculated: C 65.3; H 4.9; N 13.9%.

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