The first excited state in V and VIII (Table 2) is associated with transfer of electron density from the perfluorophenyl group (0.35 e) and the nitrogen atom (0.3 e) to the azomethine bond (0.35 e) and the phenyl ring (0.3 e). The second excited state has a similar nature. The presence of a methoxy group in the 3-phenyl ring does not fundamentally affect the nature of the electron transitions. Consequently, according to the calculated values, the perfluorophenyl group in the 1 position of the heteroring acts as a weak electron acceptor in the electronic ground state and as a rather strong electron donor with respect to the phenyl group in the first and second excited states.

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NMR SPECTRA OF PYRIMIDINES. EFFECT OF SUBSTITUENTS ON THE CHEMICAL SHIFTS OF THE "meta" PROTONS IN 2- AND 4-SUBSTITUTED PYRIMIDINES

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The chemical shifts of the protons in the even positions of the pyrimidine ring in 2- and 4-substituted pyrimidines in dimethyl sulfoxide solutions were determined. The correlation equations that link the relative chemical shifts (with allowance for corrections for the magnetic anisotropy of the substituents and the ring) with the F and R substituent constants were calculated. The ratios obtained were analyzed by comparison with the corresponding correlation equations for monosubstituted benzenes. The reasons for the significant increase in the transmission of the conjugation effects of the substituents to the even positions of the pyrimidine ring as compared with the meta positions of the benzene ring and the appreciable weakening of the conductivity of their inductive effects when the heteroring nitrogen atom is situated between a resonating proton and the substituent are discussed.

We have previously [1] studied the effect of substituents on the chemical shifts of the 5-H and 2-H protons in 2- and 5-substituted pyrimidines and have ascertained the specific characteristics of the transmission of the electronic effects of substituents to the para position in the pyrimidine ring via both inductive and conjugation mechanisms. In the present communication we examine the effect of substituents on the chemical shifts of the protons of the pyrimidine ring that are located in meta positions relative to the substituent. The measured chemical shifts of the protons in the 4 position of the ring (δ_4-H) for 2-substituted pyrimidines (series I) and in the 2 (δ_2-H) and 6 (δ_6-H) positions for 4-substituted

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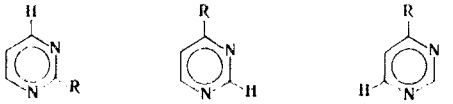
TABLE 1. Chemical Shifts of the "meta" Protons in 2- and 4-Substituted Pyrimidines (at 60 MHz)

Substituent, R,	2-Substituted pyrimidines, series I			4-Substituted pyrimidines, series II			series III		
	$\delta_{4\text{-H}}$ Hz	$\Delta\delta_{4\text{-H}}$ Hz a	$\Delta\delta'_{4\text{-H}}$ Hz a	$\delta_{2\text{-H}}$ Hz	$\Delta\delta_{2\text{-H}}$ Hz a	$\Delta\delta'_{2\text{-H}}$ Hz a	$\delta_{6\text{-H}}$ Hz	$\Delta\delta_{6\text{-H}}$ Hz a	$\Delta\delta'_{6\text{-H}}$ Hz a
$N(CH_3)_2$	499,5	29,5	26,5	507,5	44,5	41,5	487	42	39
OCH_3	516	13	10	529	23	20	510,5	18,5	15,5
CH_3	522	7	4	542	10	7	518	11	8
C_6H_5	534,5	−5,5	−2,5	555	−3	0	531,5	−2,5	0,5
H	529	0	0	552	0	0	529	0	0
F	529	0							
Cl	527	2	−8		7,5 b	−2,5		2 c	−8
Br	523,5	5,5	−7,5						
$COOCH_3$	538,5	−9,5	−13,5	562,5	−10,5	−14,5	545,5	−16,5	−20,5
SO_2CH_3	546	−17							
CN	541,5	−12,5	−18,5	564,5	−12,5	−18,5	549,5	−20,5	−26,5

a) The positive values correspond to the shift of the resonance signal to strong field. b) Calculated from the data for 4,6-dichloropyrimidine. c) Obtained by averaging the values calculated by an additive scheme for 2-substituted 4-chloropyrimidines.



I II III

pyrimidines (series II and III) are presented in Table 1. It should be noted that the relative chemical shifts of the 4-H proton ($\Delta\delta_4$-H) for the series of 2-substituted pyrimidines measured in dimethyl sulfoxide (DMSO) are close to the values presented in the literature for acetone solutions [2]; only the data for cyano and methoxycarbonyl derivatives differ somewhat.

It is known from the literature data [3, 4] that in the benzene series the effect of a substituent on the relative chemical shift of the para proton is determined primarily by electronic effects, which are transmitted along the systems of σ and π bonds and directly through the field. The effects of magnetic anisotropy do not have an appreciable influence on the shielding of the para proton, which is rather far away from the substituent. The change in the magnetic anisotropy of the aromatic ring under the influence of substituents also does not have a substantial effect. However, in the case of meta protons transmission of the electronic effect of a substituent along the system of π bonds is substantially less effective, and the effect of magnetic anisotropy of the substituent is intensified because of its drawing near to the resonating proton. In addition, the relative role of the effect of magnetic anisotropy of the aromatic ring increases because of a decrease in the electronic effect of the substituent on the shielding of the meta protons. A method for the empirical evaluation of the overall effect of the magnetic anisotropy of the substituent and the change of the anisotropy of the aromatic ring on the shielding of the meta protons in monosubstituted benzenes was proposed in [5]. Whereas these corrections are relatively small (3-4 Hz) for most substituents, they are sizeable (6-21 Hz) for the cyano group and halogen atoms.

During a comparison of the relative chemical shifts for the same derivatives of the benzene and pyrimidine series one's attention is drawn to the intensification of the effect of substituents on the shielding of the "meta" protons in pyrimidine; in a number of cases (for example, in 4-substituted pyrimidines with electron-donor substituents) it approaches the effect exerted by a substituent on the shielding of the para protons in the benzene ring. It would therefore be completely possible to disregard the effects of magnetic anisotropy in the pyrimidine series, particularly for series II and III. However, it was necessary to correct the relative chemical shifts of the meta protons with allowance for the magnetic anisotropy of the substituents and the heterocyclic ring in order to obtain an adequate picture in the comparison of the results of correlation analysis for the benzene and pyrimidine series. We made this correction by the introduction of the same anisotropic corrections that were used [5] in the benzene series. The possibility of the use of these corrections

TABLE 2. Parameters of Correlation Equation IV

Series	$\Delta\delta_H$	γ_I	γ_R
Benzene series[a]	$\Delta\delta_{p\text{-}H}$	1,0	1,0
	$\Delta\delta'_{m\text{-}H}$	1,0	0,3
Pyrimidine series			
I	$\Delta\delta'_{4\text{-}H}$	0.8	0,6
II	$\Delta\delta'_{2\text{-}H}$	0,6	0,9
III	$\Delta\delta'_{6\text{-}H}$	1,1	0,9

a) Data from [5].

in the pyrimidine series follows from the data on the small degree of perturbation of six-membered aromatic systems when the methyl group is replaced by a nitrogen heteroatom [6] and the closeness of the "ring currents" of benzene and pyrimidine [7, 8], as well as from a comparison of the geometrical parameters of benzene and pyrimidine molecules [9]. In the case of phenylpyrimidines the anisotropic correction for the phenyl group was calculated by the method in [10] with allowance for the geometries of the benzene and pyrimidine rings [9], assuming a torsion angle of about 40°, in analogy with biphenyl [11] and phenylpyridines [12]. The "corrected" relative chemical shifts of the meta protons ($\Delta\delta'$) are presented in Table 1. The chemical shifts for 2-fluoro- and 2-methylsulfonylpyrimidines were not corrected because of the lack of the necessary data, and the corresponding values therefore were not examined in the correlation analysis.

We separated the electronic effects of the substituents into their inductive and conjugation components by two-parameter correlation with the F and R substituent constants [13]:

$$\Delta\delta'_{4\text{-}H} = -1.1 - 24.8F - 32.3R;\ R = 0.996,\ s = 1.4\ \text{Hz} \quad (I)$$

$$\Delta\delta'_{2\text{-}H} = -0.7 - 19.0F - 48.1R;\ R = 0.999,\ s = 1.2\ \text{Hz} \quad (II)$$

$$\Delta\delta'_{6\text{-}H} = -0.2 - 35.8F - 47.1R;\ R = 0.999,\ s = 1.0\ \text{Hz} \quad (III)$$

From a comparison of the correlation equations obtained in this research it may be concluded that the contribution of the R component predominates for series II and III and that consequently the substituents in the 4 position display exalted +M effects. In turn, the contribution of the F component is appreciably lower for series I and II than for series III, i.e., the inductive effect of a substituent is weakened if the substituent and the resonating proton are separated by a heterocyclic nitrogen atom. The ratios may be analyzed more rigorously by comparison of the investigated series with a standard correlation series. We selected the dependence of the relative chemical shift of the para protons on the F and R substituent constants in monosubstituted benzenes [5] as the standard correlation series. In this case the transmission of the electronic effects of substituents via inductive and conjugation mechanisms from one even position of the pyrimidine ring to another even position can be correlated with the transmission of the same effects to the para position of the benzene ring (see [1]) by means of the corresponding transmission factors γ_I and γ_R (Table 2):

$$\Delta\delta_H = -32.3\,(\gamma_I F + 1.63\gamma_R R). \quad (IV)$$

For comparison, the transmission factors that characterize transmission of the electronic effects of substituents to the meta position, which were calculated by means of the previously found correlation dependence of the chemical shifts of the meta protons on the F and R constants [5], are also presented in Table 2. It is important to note that the degrees of transmission of the inductive effects of substituents to the meta and para positions of the benzene ring virtually coincide, whereas the degree of transmission of their conjugation effects in the meta position is weakened by a factor of about three as compared with the para position; this is in good agreement with the data in [14]. This fact may serve as an indirect confirmation of the correctness in the determination of both the anisotropic and electronic effects of substituents that are transmitted to the meta positions of the benzene ring.

The transmission of the electronic effect of substituents along the system of π bonds from one even position to another is intensified considerably in the pyrimidine ring as compared with the meta position in the benzene ring and in the case of series II and III even approaches the transmission for the para position. This additional "indirect" conjugation of the substituent with the "reaction center" in the meta position relative to it in a series

of six-membered nitrogen-containing heteroaromatic systems is ascribed in the literature to electronic interaction of the +M substituent with the electron-acceptor o- or p-oriented nitrogen heteroatoms; this interaction is most effective for the second combination [15]. In the pyrimidine series ortho—para interaction of a substituent with the nitrogen heteroatom turns out to be more effective for 4-substituted derivatives (series II and III) than ortho—ortho interaction for 2-substituted compounds (series I).

A large amount of data that provide evidence that the inductive effects of substituents, at least for most substituents, have electrostatic natures and are transmitted to a rather remote reaction center mainly through the field [16, 17] has been accumulated. The geometry of the molecule and the macroscopic properties of the medium therefore are important for the transmission of inductive effects. Dewar and Grisdale [16] have pointed out the existence of an inverse proportional dependence of the field effect on the distance between the point dipole of the substituent and the reaction center in the molecule. Slight reinforcement (by a factor of 1.1) of the indicated effect might have been expected for the examined series of pyrimidines from a comparison of the distances between the meta positions in benzene and between the even positions in pyrimidine [9] ($r_{meta}:r_{2,4}:r_{4,6}$ = 1.0:0.92:0.91). This value is in agreement with a transmission factor γ_1 for series III but differs considerably for series I and II (Table 2). In all compounds of series I and II the resonating proton and the substituent are separated by a nitrogen heteroatom which, due to the dipole of the free electron pair, creates an electrical field that is capable of weakening the electrostatic interaction of the substituent with the proton. We have also observed the same effect of weakening of the inductive effect of substituents on the chemical shift of 2-H protons in a series of 5-substituted pyrimidines [1]. Similar observations were previously made in the pyridine [18, 19] and pyrazine [18] series. In all likelihood, the specific character of the nitrogen heteroatoms, which consists in weakening of the inductive effect of substituents on the chemical shift of the aromatic protons, will also be manifested in other six-membered nitrogen-containing heteroaromatic systems.

EXPERIMENTAL

The PMR spectra of 4 mole % solutions of the compounds in dimethyl sulfoxide DMSO were recorded with a Varian A 60/56 A spectrometer (60 MHz) at 37-38°C with the ^{13}C—H satellite of DMSO (221 Hz from the signal of tetramethylsilane) as the internal standard. The chemical shifts were determined with an accuracy of ±0.5 Hz. The DMSO was dried over molecular sieves. The commercial-grade pyrimidine [Chemapol (Czechoslovakian Socialist Republic)] was distilled prior to recording of the spectra. 2-Methylsulfonylpyrimidine was obtained by the method in [20], and the 4-cyano- and 4-methoxycarbonylpyrimidines were obtained by the method in [21]. The constants and methods for the preparation of 2-methoxycarbonylpyrimidine are presented in [22], and comparable information for the remaining pyrimidine derivatives is presented in [23].

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ANALOGS OF PYRIMIDINE MONO- AND POLYNUCLEOTIDES.

VI.* PHOSPHATES OF 1-(1,4-DIHYDROXY-2-PENTYL)THYMINE AND 1-(1,3-DIHYDROXY-2-PROPYL)URACIL

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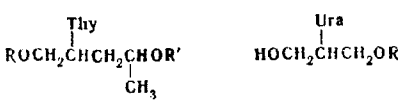
The corresponding monophosphates, cyclophosphates, and α,ω-diphosphates were obtained by phosphorylation of 1-(1,4-dihydroxy-2-pentyl)thymine, 1-(1,3-dihydroxy-2-propyl)uracil, and their derivatives with selective protection of one of the hydroxyl groups. 2-Cyanoethyl phosphate (CEP) in the presence of N,N'-dicyclohexylcarbodiimide (DCC), polyphosphoric acid, and pyrophosphoryl chloride were used as phosphorylating agents. The dependence of the yields of the products of phosphorylation of 1-(1,4-dihydroxy-2-pentyl)thymine with CEP on the ratio of the reacting substances and the reaction time was studied. The monophosphates were cyclized under the influence of DCC. In the case of 1-(1,3-dihydroxy-2-propyl)uracil 1-phosphate a dimeric phosphate was obtained in addition to a cyclophosphate. The acid hydrolysis of the cyclophosphates was investigated.

The phosphates of 1-(1,4-dihydroxy-2-butyl)thymine (I) that we synthesized in [3, 4] were used as monomers for the preparation of analogs of oligothymidylic acid, which displayed interesting biological properties [5]. However, these oligomers have the disadvantage that their structures are indeterminate, since a 1'—1, 1'—4', or 4'—4' bond may be realized during polycondensation.

Our research was directed toward a search for new dihydroxyalkyl derivatives of pyrimidine bases, on the bases of which the synthesis of oligomers with a more regular structure is possible.

The present paper is devoted to the synthesis of phosphates of 1-(1,4-dihydroxy-2-pentyl)thymine (IIa) [6] and 1-(1,3-dihydro-2-propyl)uracil (IIIa) [7]. The presence in diol IIa of primary and secondary hydroxyl groups facilitates the selective phosphorylation with the use of, respectively, protected derivatives IIb,c, and the symmetrical character of the dihydroxyalkyl group in IIIa makes it possible to obtain only one monophosphate (Vb).



II a-c III a,b

II a R=R'=H; b R=C(C6H5)3, R'=H; c R=H, R'=COCH3;
III a R=H; b R=C(C6H5)3

*See [1] for communication V; see [2] for a preliminary communication.
†Deceased.

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