NMR SPECTRA OF PYRIMIDINES. EFFECT OF SUBSTITUENTS ON THE CHEMICAL SHIFT OF THE PROTONS OF THE AMINO GROUP OF p-SUBSTITUTED 2- AND 5-AMINOPYRIDINES AND ANILINES

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The chemical shifts of the protons of the amino groups of p-substituted anilines and 2- and 5-aminopyrimidines in dimethyl sulfoxide were measured, and their dependence on the inductive and conjugative constants of the substituents was studied. On the basis of an analysis of the correlation equations it was concluded that there is a rather close similarity in the pyrimidine and benzene rings with respect to their conductivity of the inductive effect of substituents in the para position. A difference in the conductivity of the electronic effects of substituents over the system of π bonds of the pyrimidine ring as a function of the relative orientation of the substituents and the reaction center is demonstrated.

In a previous study [1, 2] of the PMR spectra of substituted pyrimidines we ascertained the dependence of the magnitude of the chemical shift of the protons in the 2 and 4 positions of the pyrimidine ring on the inductive and conjugative effects of the substituents; we also noted appreciable weakening of the inductive effect if the resonating proton and the substituent are separated by a heterocyclic nitrogen atom. At the same time, it was demonstrated in [3] that a similar effect is not displayed with respect to the protons of the amino group in analogous series of 2- and 4-aminopyrimidines with substituents in even-numbered positions of the pyrimidine ring. To confirm the general character of this conclusion we examined the electronic effects of substituents on the relative chemical shift of the protons of the amino group [$\Delta\delta(NH_2)$] (Table 1) in series of 2- and 5-aminopyrimidines with substituents formally located in the para position relative to the amino group, and the dependences obtained were compared with the dependences for a series of p-substituted anilines. Our measured values of the chemical shifts of the protons of the amino group for toluidine, anisidine, bromoaniline, and nitroaniline were in good agreement with the data in [4], while the difference for unsubstituted aniline was quite appreciable (6 Hz); we did not verify the chemical shifts for the chloro and ethoxy derivatives of aniline but took them from [4]. The set of substituents in all of the series makes it possible to not only find a correlation link between the electronic nature of the substituent and the magnitude of the relative chemical shift of the protons of the amino group but also to compare the latter with one another for the same substituted compounds in different series. Since derivatives with a nitro group in even-numbered ring positions are unknown in the pyrimidine series, we additionally included the trifluoromethyl derivative in place of the nitro derivative in the 5-aminopyrimidine series.

For a quantitative analysis of the contributions of the inductive and conjugative components to the overall electronic effect of a substituent on the magnitude of the relative chemical shift of the protons of the amino group we calculated the coefficients of the two-parameter correlation equations for the indicated I-III series (Table 2) by the method of least squares. We used the σ_I and σ_R^- substituent constants as the variable parameters. The selection of the σ_R^- constants was based on the data in [4-6], which indicate the necessity for the use of the nucleophilic substituent constants in correlations for series in which

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TABLE 1. Chemical Shifts (Hz) of the Protons of the Amino Group of p-Substituted Anilines and Aminopyrimidines in Dimethyl Sulfoxide at 60 MHz

Substituent	Anilines		2-Aminopyrimidines		5-Aminopyrimidines	
	$\delta(NH_2)$	$\Delta\delta(NH_2)$*	$\delta(NH_2)$	$\Delta\delta(NH_2)$*	$\delta(NH_2)$	$\Delta\delta(NH_2)$*
$N(CH_3)_2$	259	35	350	39	263	64
OC_2H_5	270†	24	365	24	292	35
OCH_3	271†	23	365	24	294	33
CH_3	282	12	375	14	311	16
H	294	0	389	0	327	0
F	294	0	391	−2	325	2
Cl	309†	−15	402	−13	340	−13
Br	310	−16	409	−20	341	−14
CF_3					374	−47
$COOCH_3$	340	−46			378	−51
$COOC_2H_5$	353	−59	444	−55		
CN	364	−70	460	−71	394	−67
NO_2	398	−104	488	−99		

*The positive values corresponding to a shift of the signal to strong field.
†According to the data [4].

TABLE 2. Parameters of the Correlation Equation $\Delta\delta(NH_2) = \rho_I\sigma_I + \rho_R\sigma_R + c$

Series	ρ_I	ρ_R	c	r	s	n	Transmission factors	
							γ_I	γ_R
Anilines (I)	−72,6	−80,6	0,4	0,995	4,6	12	1,00	1,00
2-Aminopyrimidines (II)	−74,8	−80,4	1,4	0,998	3,0	11	1,03	1,00
5-Aminopyrimidines (III)	−77,7	−89,7	7,2	0,983	8,2	11	1,07	1,11

the reaction center is the amino group; for most +C substituents, such as halogens and alkoxy groups, the σ_R^- constants correspond numerically to the σ_R constants [7], whereas in the case of the dimethylamino group the σ_R^- constant corresponds to the σ_R^0 constant. We found that the parameters of the correlation equations for the I and II series remain virtually unchanged, except for the point for the dimethylamino derivative, whereas they do change for the III series but not very substantially.

A comparison of the correlation equations for the series of 2- and 5-aminopyrimidines (II and III) and anilines (I) as the standard series makes it possible to use the transmiission factors for the inductive (γ_I) and conjugative (γ_R) effects of the substituents in the pyrimidine ring (Table 2). Our data indicate sufficiently close similarity in the pyrimidine and benzene rings with respect to the conductivity of the inductive effect of the substituents in the para position. Considering the substantial contribution of the field component to the inductive effect, one may expect its dependence on steric factors, which are determined by the relative orientation of not only the substituent and the reaction center but also the nitrogen atoms of the heterocyclic ring. The observed difference in the conductivity of the inductive effect of the substituents from the 5 position of the pyrimidine ring to the shielding of the aromatic 2-H proton (γ_I 0.7 [1]) and the protons of the amino group (γ_I 1.0) in the 2 position is probably associated with the greater distance of the latter from the heterocyclic nitrogen atoms.

However, the conductivity of the electronic effect of the substituents along the system of π bonds of the pyrimidine ring differs somewhat depending on the relative orientation of the substituent and the amino group. Thus the conductivity of the conjugative effect of

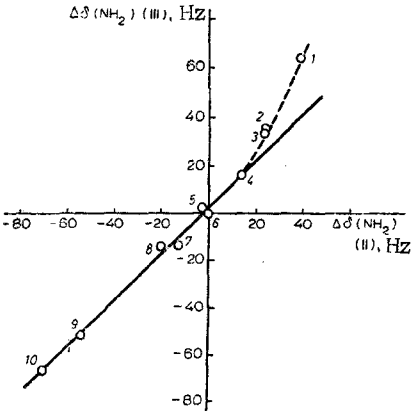

Fig. 1. Relative chemical shifts [$\Delta\delta(NH_2)$] of substituted 2-aminopyrimidines (II) and 5-aminopyrimidines (III) with $N(CH_3)_2$ (1), OC_2H_5 (2), OCH_3 (3), CH_3 (4), F (5), H (6), Cl (7), Br (8), $COOCH_3$ and $COOC_2H_5$ (9), and CN (10) substituents (the numbers correspond to the points on the graph).

substituents from the 5 position of the pyrimidine ring to the 2-amino is close to the conductivity of the same effect in the benzene ring (γ_R 1.0). However, its conductivity is somewhat intensified in the case of transmission from the 2 position of the pyrimidine ring to the 5-amino group (γ_R 1.1). This conclusion is in agreement with our data [1] on the conductivity of electronic effects obtained during a study of the PMR spectra of substituted pyrimidines with aromatically bonded protons as the "reaction" center, despite the substantial difference in these series with respect to the character of the substituent with the reaction center — the existence of direct polar conjugation in the case of aminopyrimidines and the lack of such conjugation for substituted pyrimidines.

In the examination of the data in Table 1 one's attention is drawn to the anomalously large shift to strong field of the signal of the protons of the amino group of 5-amino-2-dimethylaminopyrimidine, which cannot be due only to intensification of the conductivity of the conjugative effect of the dimethylamino group through the pyrimidine ring. It is apparent from the graph in Fig. 1, in which the relative shifts of the protons of the amino group for the same substituted compounds in both pyrimidine series (II and III) are compared, that a linear dependence is retained only in the case of substituents with a —C effect (CN, CF_3, and COOR) or with a small +C effect (Cl, Br, and CH_3). However, the points that characterize the substituents with a strong +C effect (OCH_3, OC_2H_5, and $N(CH_3)_2$) deviate considerably form the line depicted in Fig. 1 (for comparison, let us point out that deviations from linearity are not observed in the case of comparison of the data for series I and II). It follows from this that not only the conductivity of the electronic effects but also the very character of the interaction of the substituent with the reaction center change in the III series. The decrease in the electronic requirement of the aromatic system with respect to the +C substituents that arises under the influence of the +C reaction center is partially compensated in the III series by the acceptor character of the two ortho-oriented (relative to the substituents) nitrogen atoms of the pyrimidine ring. Correspondingly, one should expect weakening of the electron-donor capacity of this aromatic system with respect to substituents with a strong —C effect (CN, CF_3, and COOR). In fact, the experimentally found values of the relative chemical shifts in the III series are best described within the framework of a correlation equation in which the conjugative constants of the substituents take on values that are intermediate between σ_R and σ_R^-:

$$\Delta\delta(NH_2) = -77.9\sigma_I - 97.7(\sigma_R + \sigma_R^-)/2 + 1.2;\ r = 0.998;\ s = 2.6.$$

However, the coefficients in this equation differ only insignificantly from those presented in Table 2 for the III series.

EXPERIMENTAL

The PMR spectra of solutions (4 mole %) of the compounds in dimethyl sulfoxide (DMSO) were recorded with a Varian A 60/56 A spectrometer (60 MHz) at 37-38°C. The ^{13}C—H satellite of DMSO [221 Hz from the signal of tetramethylsilane (TMS)] was used as the internal standard. The chemical shifts were determined with an accuracy of ±0.7 Hz. The DMSO was dried over molecular sieves.

2-Amino-5-dimethylaminopyrimidine. A 0.22-g (1.4 mmole) sample of 2-chloro-5-dimethylaminopyrimidine was heated in an autoclave in 15 ml of ethanol saturated with ammonia at 220°C for 35 h, after which the mixture was evaporated in vacuo. Water (2 ml) was then added, and the mixture was extracted with $CHCl_3$. The extract was evaporated to dryness, and the residue was sublimed in vacuo. The product was purified by thin-layer chromatography (TLC) on silica gel [elution with ethyl acetate–ethanol (20:1)]. The lower zone (which was detected in UV light) was collected and eluted with ethanol. The eluate was evaporated, and the residue was crystallized from benzene–hexane (1:1) to give 0.12 g (62%) of a compound with mp 112-114°C. Found: C 52.5; H 7.25; N 40.8%. $C_6H_{10}N_4$. Calculated: C 52.5; H 7.30; N 40.6%.

5-Amino-2-methoxypyrimidine. A 0.13-g (1 mmole) sample of 2-chloro-5-aminopyrimidine was heated in an autoclave with a solution of 0.03 g (1.3 mg-atoms) of sodium in 3 ml of methanol at 180-200°C for 12 h, after which the mixture was evaporated in vacuo, and the residue was treated with 5 ml of water. The pH of the solution was adjusted to 8 with dilute HCl, after which it was extracted with ethyl acetate. The extract was passed through Al_2O_3 (activity II) and eluted with $CHCl_3$. The eluate was evaporated to dryness to give 0.06 g (50%) of a product with mp 117.5-118.5°C [from petroleum ether–$CHCl_3$ (1:1)] (mp 119-120°C [10]).

5-Amino-2-ethoxypyrimidine. A 0.39-g (3 mmole) sample of 2-chloro-5-aminopyrimidine was heated in an autoclave with a solution of 0.09 g (4 mg-atoms) of sodium in 5 ml of ethanol at 190-200°C for 12 h, after which the mixture was evaporated in vacuo, and the residue was treated with 5 ml of water. The pH of the solution was adjusted to eight with dilute HCl and extracted with ethyl acetate. The extract was evaporated, and the product was purified by TLC on silica gel [elution with ethyl acetate–$CHCl_3$ (1:1)]. The lower zone (which was detected by means of UV light) was collected by elution with ethyl acetate, and the eluate was passed through a layer of Al_2O_3 and evaporated. The residue was crystallized from CCl_4 with activated charcoal and sublimed in vacuo to give 0.13 g (30%) of a product with mp 85-86°C. Found: C 51.7; H 6.59; N 30.6%. $C_6H_9N_3O$. Calculated: C 51.8; H 6.52; N 30.2%.

5-Amino-2-methoxycarbonylpyrimidine. Dry HCl was bubbled through a refluxing suspension of 0.42 g (3 mmole) of 5-aminopyrimidine-2-carboxylic acid [10] in 20 ml of methanol for 3 h, after which the solution was evaporated in vacuo, and the residue was treated with a saturated solution of K_2CO_3 and extracted repeatedly with $CHCl_3$. The extract was evaporated, and the reaction product was purified by TLC on silica gel [elution with $CHCl_3$–ethanol (10:1)]. The lower zone (which was detected in UV light) was collected by elution with ethanol, the eluate was evaporated, and the residue was sublimed in vacuo to give 0.10 g (22%) of a product with mp 193-195°C (in a capillary). Found: C 46.5; H 4.67; N 27.2%. $C_6H_7N_3O_2$. Calculated: C 47.0; H 4.61; N 27.4%.

5-Amino-2-trifluoromethylpyrimidine. A mixture of 2.13 g (9.2 mmole) of 5-amino-4,6-dichloro-2-trifluoromethylpyrimidine, 0.40 g (10 mmole) of MgO, and 0.20 g of a 10% Pd/C catalyst in 30 ml of 80% ethanol was hydrogenated with hydrogen at 40-50°C. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration and washed with ethanol. The filtrate was evaporated in vacuo, and the residue was extracted with ethyl acetate. The extract was evaporated to dryness, and the residue was crystallized from methanol and sublimed in vacuo to give 0.65 g (43%) of a product with mp 195-197°C (in a capillary). Found: C 36.7; H 2.54; N 25.5%. $C_5H_4F_3N_3$. Calculated: C 36.8; H 2.47; N 25.8%.

The remaining pyrimidine derivatives used in this research were obtained by known methods, and their constants were in agreement with the constants presented in the literature [8-10].

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SYNTHESIS OF 3-CYANO-4,6-BIS(METHYLTHIO)PYRAZOLO[3,4-d]PYRIMIDINE 1-RIBOSIDE

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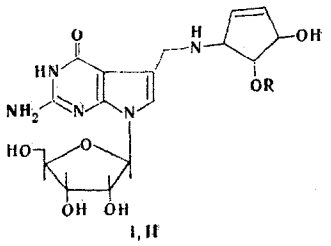
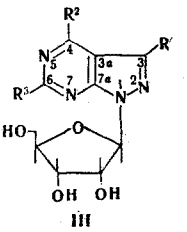
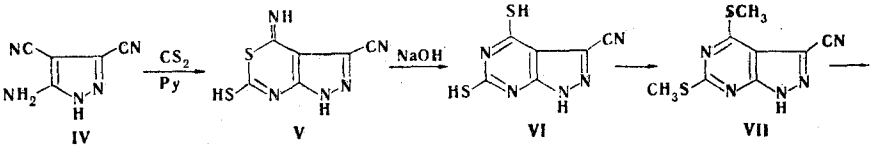
3-Cyano-4,6-bis(methylthio)pyrazolo[3,4-d]pyrimidine was synthesized by cyclization of 3,4-dicyano-5-aminopyrazole with CS_2 in pyridine with subsequent Dimroth rearrangement and methylation of the resulting 3-cyano-4,6-dimercaptopyrazolo[3,4-d]-pyrimidine with methyl iodide. Glycosylation of the product by fusion with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in the presence of iodine gave 1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-3-cyano-4,6-bis(methylthio)pyrazolo[3,4-d]pyrimidine, the deacetylation of which with a 1% solution of hydrogen chloride in methanol led to 3-cyano-4,6-bis(methylthio)pyrazolo[3,4-d]pyrimidine 1-riboside. The structures of the compounds were established by IR, UV, circular dichroism, PMR, and ^{13}C NMR spectroscopy.

The high biological activity of toyocamycin and sangivamycin, which are pyrrolopyrimidine analogs of adenosine that contain substituents in the pyrrole ring, is well-known [1]. Considerably less study has been devoted to guanosine analogs with substituents in the five-membered ring. In the 7-desazaguanosine series nucleosides Q (I) and Q* (II) belong to this class [2, 3]. The preparation of pyrazolopyrimidine analogs of purine nucleosides with the general formula III that contain substituents in both the pyrazole and pyrimidine rings and are simultaneously analogs of toyocamycin (or sangivamycin) and guanosine seems of interest.

In the present paper we describe the synthesis of 3-cyano-4,6-bis(methylthio)pyrazolo-[3,4-d]pyrimidine (VI) and its 1-riboside (X), which are key compounds for the preparation of trisubstituted pyrazolo[3,4-d]pyrimidines and their ribosides with the general formula III.







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