^{19}F NMR spectrum (CCl_4): 1.00 ppm (s, CF_3). Found: C 47.2; H 4.3; N 11.7%. $C_{14}H_{14}Cl_2F_3N_3$. Calculated: C 47.8; H 4.0; N 11.9%.

N-Mesitylbenzimidoyl Chloride (VII). In analogy with [4], a mixture of 3.6 g (0.015 mole) of N-mesitylbenzamide and 4.16 g (0.02 mole) of PCl_5 in 30 ml of benzene was refluxed for 1 h until HCl evolution ceased, after which the mixture was cooled and SO_2 was passed through it to remove the excess PCl_5. The solvent was evaporated, and the residue was distilled *in vacuo* to give 2.78 g (72%) of a product with bp 122-123°C (0.06 mm) and n_D^{20} 1.6021. IR spectrum (CCl_4): 1670 cm^{-1} (C=N). PMR spectrum (CCl_4): 7.43-8.30 (5H, m, C_6H_5), 6.97 (2H, s, CH), 2.43 (3H, s, CH_3), and 2.20 ppm (6H, s, CH_3). Found: C 74.3; H 6.0; N 5.5%. $C_{16}H_{16}ClN$. Calculated: C 74.6; H 6.3; N 5.4%.

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SYNTHESIS AND REACTIVITIES OF 5-HYDROXYPYRIMIDINE 1-OXIDES IN ELECTROPHILIC SUBSTITUTION

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1-Oxides of a series of 5-hydroxypyrimidine derivatives were synthesized, and their reactivities in electrophilic-substitution reactions (aminomethylation) as compared with 3-hydroxypyridine 1-oxides were investigated. It is shown that the activity of the 5-hydroxypyrimidine ring in the case of ring substitution increases as a result of N-oxidation, whereas methyl groups become less active.

Until recently, 5-hydroxypyrimidine 1-oxides were an uninvestigated class of nitrogen-containing heteroaromatic compounds, and their direct synthesis by N-oxidation of the pyrimidine ring had not been described. Data on the N-oxidation of other pyrimidine derivatives by the action on them of hydrogen peroxide and acetic acid [1, 2] (sometimes in the presence of a catalyst [3]) and permaleic and m-chloroperbenzoic acids [4] have been presented in the literature; tert-amyl hydroperoxide in the presence of molybdenum salts also serves as a good reagent for these purposes [5]. N-Oxidation, like protonation, of one of the nitrogen atoms of the pyrimidine ring significantly decreases the basicity of the second nitrogen atom. The preparation of N,N'-dioxides of the pyrimidine ring without introducing electron-donor substituents into the molecule is apparently impossible for this reason — the presence of two amino groups makes this reaction possible [6]. We noted that steric factors sometimes hinder the N-oxidation of pyrimidine derivatives. The oxidation of a substituted 2-phenylpyrimidine did not lead to the production of the corresponding N-oxide, 4-phenylpyrimidine gave only the 1-oxide, and a mixture of 1- and 3-oxides was obtained from 4-methylpyrimidine [4, 7].

We have synthesized a number of N-oxides that are derivatives of 5-hydroxypyrimidine (see Table 1), including 2-phenyl- and 2-tert-butyl-4,6-dimethyl-5-hydroxypyrimidine 1-oxides, which constitutes evidence for the possibility of overcoming the steric hindrance created by the 2-phenyl group and the even bulkier 2-tert-butyl group in N-oxidation. In

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TABLE 1. Characteristics of the Synthesized 5-Hydroxypyrimidine 1-Oxides II

Compound	R	mp, °C	R_f	PMR spectrum, ppm			Found, %		Empirical formula	Calc., %		Yield, %
				2-R	4-R	6-R	C	H		C	H	
II[a]	H	202—204[b] (subl.)	0,54[c]	8,32 (1H, d)	7,82 (1H, d)	7,97 (1H, q)	42,8	3,7	$C_4H_4N_2O_2$	42,9	3,6	84
IIa	H	187—189[b] (subl.)	0,32[b]	8,23 (1H, s)	2,42 (3H, s)	2,36 (3H, s)	51,3	5,8	$C_6H_8N_2O_2$	51,4	5,8	96
IIb	Me	193—195[b] (subl.)	0,39[b]	2,53 (3H, s)	2,43 (3H, s)	2,36 (3H, s)	54,3	6,6	$C_7H_{10}N_2O_2$	54,5	6,5	94
IIc	*i*-Pr	159—161[d]	0,48[b]	2,30 (6H, d); 3,10 (1H, q)	2,36 (3H, s)	2,43 (3H, s)	59,2	7,6	$C_9H_{14}N_2O_2$	59,4	7,7	82
IId	*t*-Bu	184—186[e]	0,53[f]	1,02 (9H, s)	2,51 (3H, s)	2,49 (3H, s)	61,3	8,1	$C_{10}H_{16}N_2O_2$	61,2	8,2	76
IIe	C_5H_{11}	115—117	0,28[f]	0,90 (3H, m); 1,37 (4H, m); 1,77 (2H, m); 2,96 (2H, m)	2,42 (2H, s)	2,37 (3H, s)	62,8	8,7	$C_{11}H_{18}N_2O_2$	62,8	8,6	95
IIf	CH_2Ph	213—214[b]	0,25[g]	3,70 (2H, s); 7,40 (3H, m); 7,90 (2H, m)	2,42 (3H, s)	2,38 (3H, s)	69,7	6,0	$C_{13}H_{14}N_2O_2$	67,8	6,1	92
IIg	Ph	259—260[h]	0,12[g]	7,48 (3H, m); 8,02 (2H, m)	2,50 (3H, s)	2,45 (3H, s)	66,8	5,8	$C_{12}H_{12}N_2O_2$	66,7	5,6	68

[a]5-Hydroxypyrimidine 1-oxide. [b]Acetone. [c]Acetone—methanol (1:1). [d]Methanol—ethyl acetate. [e]Methanol—acetone. [f]Ethyl acetate. [g]Benzene—acetone (1:1). [h]Methanol.

the case of oxidation with perbenzoic acid some N-oxides can be obtained in yields that are close to quantitative; however, the complexity of dispensing the reagent in connection with the low stability of perbenzoic acid and its inadequate activity (only traces of the 1-oxide can be observed in the oxidation of the 2-tert-butyl derivative) compelled us to turn to a more stable, active, and conveniently recoverable oxidizing agent, viz., p-nitroperbenzoic acid. The reaction can be carried out in both chloroform and in ethyl acetate or acetone.

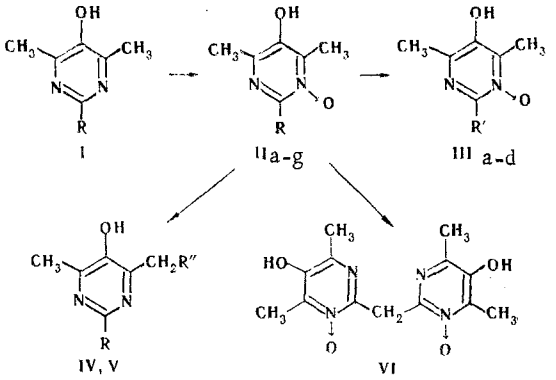
The two doublets with $J_{26} = 1.8$ and $J_{46} = 2.5$ Hz in the PMR spectrum of 5-hydroxypyrimidine 1-oxide were assigned to the 2-H and 4-H protons, respectively, and the quartet was assigned to the 6-H proton. The assignment of the 4-H and 6-H signals was made on the basis of the fact that oxidation of the nitrogen atom causes an increase in the meta J_{26} spin—spin coupling constant (SSCC), whereas the J_{24} value is close to zero, as in the case of 5-hydroxypyrimidine. The CH_3 groups in 4,6-dimethyl-5-hydroxypyrimidine 1-oxide are unequivalent; the signal at strong field was assigned to the methyl group in the ortho position relative to the N-oxide group on the basis of a comparison of the chemical shifts of the methyl groups of 2-methyl- and 6-methyl-3-hydroxypyridine with the corresponding N-oxides [8, 9]. The introduction of various substituents (Me, iso-Pr, tert-Bu, C_5H_{11}, CH_2Ph, and Ph) in the 2 position of the pyrimidine ring is accompanied by the development in certain parts of the PMR spectra of new signals due to the protons of the substituent (see Table 1).

In the case of 3-hydroxypyridine 1-oxides we established that the introduction of an N-oxide group increases the reactivity of the ring in electrophilic substitution: The presence of an N-oxide group facilitates deuterium exchange of all of the reactive protons as compared with the unoxidized base; the effective rate constant for exchange of the 2-H proton is greater by a factor of 25 than in 3-hydroxypyridine [10]. Similarly, the aminomethylation of 3-hydroxypyridine 1-oxide proceeds under milder conditions than in the case of unoxidized bases [11].

We showed that, as in the case of 3-hydroxypyridine [10], the introduction of an N-oxide group into 4,6-dimethyl-5-hydroxypyrimidine increases the reactivity of the ring 2 position. Thus the effective rate constant for deuterium exchange of the 2-H proton of I (R = H) is an order of magnitude lower than for N-oxide IIa. At the same time, exchange of the protons of the methyl groups in the case of the N-oxide proceeds at a rate that is lower by a factor of three than in the case of the unoxidized compound.

We were able to establish that in the 5-hydroxypyrimidine series the activities of the 1-oxides in the case of aminomethylation in the ring also increase as compared with the unoxidized form; this is expressed in the decrease in the reaction time and the lower reaction temperature. Aminomethylation at the methyl groups, on the other hand, proceeds less successfully with the loss of selectivity. Thus the reaction of IIa (R = H) with methylenemethoxymorpholine in dioxane is complete after 2 min at 70°C with the formation of Mannich

base IIIa, whereas heating at 100°C for 2 h is required for pyrimidine I (R = H) [13]. The N-methylol derivative, which was obtained from L-proline methyl ester, gives aminomethyl derivative IIc, which has optical activity. Pyrimidine I (R = H) does not undergo this reaction under the same conditions. It is known that the aminomethylation of this compound in a mixture of formalin with a secondary amine leads to the production of derivatives involving the methyl group, whereas in an anhydrous medium treatment with paraformaldehyde with a secondary amine in the presence of triethylamine gives a ring-substitution product [12]. However, when the Mannich condensation is carried out with N-oxide IIa in an aqueous medium, it leads to the production of a mixture of products of substitution in the side chain and the ring; this constituted evidence for an increase in the activity of the 2 position of the pyrimidine ring and, in part, for a decrease in the reactivity of the methyl group. Attempts to obtain aminomethyl derivatives of IIa by the action of paraformaldehyde and a secondary amine in the presence of triethylamine led to the production of methylenebis[(4,6-dimethyl-5-hydroxy-2-pyrimidine) 1-oxide] (VI) as the only reaction product in a yield that was close to quantitative. The same results were also obtained in the absence of a secondary amine, i.e., a side (in the general sense) reaction involving crosslinking of two pyrimidine molecules in the 2 position through a methylene bridge, which is catalyzed by triethylamine, takes place when free formaldehyde is present in the reaction mixture. This fact also constitutes evidence for activation of the pyrimidine ring due to N-oxidation, since a reaction that is not realized in the case of the unoxidized compound becomes possible.



III a R′= morpholinomethyl; b R′ = piperidinomethyl; c R′ = 2-carbomethoxypyrrolidinomethyl; d R′=$CH_2N(CH_3)_2$; IV R=H, R″=$CH_2N(CH_3)_2$; V R=CH_3, R″=$CH_2N(CH_3)_2$

Thus the results of a study of the aminomethylation of substituted 5-hydroxypyrimidine 1-oxides provide evidence for the dual effect of the N-oxide group. On the one hand, the N-oxide group of the pyrimidine ring increases its reactivity in electrophilic substitution, whereas on the other hand, a passivating effect of the N-oxide group on the ability of the methyl groups of the side chain to undergo condensation reactions in weakly acidic media was noted.

EXPERIMENTAL

The PMR spectra of 8-10% solutions of the compounds in D_2O and CD_3OD were recorded with a Varian HA-100 spectrometer with hexamethyldisiloxane as the standard. Column chromatography was carried out on 40/100 μ silica gel (Czechoslovakian SSR), and thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates.

5-Hydroxypyrimidine was obtained by the method in [14], and the 2-R-4,6-dimethyl-5-hydroxypyrimidines were obtained by the method in [15].

Synthesis of Substituted 5-Hydroxypyrimidine 1-Oxides (II). 5-Hydroxypyrimidine I (1 mmole) was oxidized in solution in 10 ml of acetone at 25-40°C by the addition of 1.5 mmole of powdered p-nitroperbenzoic acid* [16] with stirring with a magnetic stirrer. After 2-12 h, the N-oxide began to precipitate from the reaction mixture; for complete precipitation, the suspension was placed in a refrigerator. The crystals were removed by filtration, washed with cold acetone, and dried. The filtrates were combined and evaporated, and the residue was passed through a column packed with silica gel. Workup of the eluate after discarding the first portion gave an additional amount of the 1-oxide.

*The reagent contained 92-96% of the principal substance (established by iodometric titration).

The purity of the compounds obtained was monitored by chromatography. Where necessary, their further purification was carried out by vacuum sublimation at 140-160°C (0.5 mm, in a stream of an inert gas in some cases) and by recrystallization.

See Table 1 for the constants and yields of oxides II.

2-Morpholinomethyl-4,6-dimethyl-5-hydroxypyrimidine 1-Oxide (IIIa). A mixture of 0.28 g (2 mmole) of IIa, 2 ml of freshly prepared N-methoxymethylmorpholine, and 5 ml of dry dioxane was heated to 70°C. After 2 min, the mixture was allowed to cool to 20°C in air. After 12 h, the crystalline precipitate was removed by filtration and washed with 1 ml of dioxane to give 0.30 g (63%) of a product with mp 175-177°C (dec., from dioxane). PMR spectrum: 2.38 (3H, s, 6-CH_3), 2.43 (3H, s, 4-CH_3), 1.31 (4H, m, CH_2NCH_2), 2.71 (4H, m, CH_2—O—CH_2), and 3.95 ppm (2H, s, —CH_2—N). Found: C 55.4; H 7.3%. $C_{11}H_{17}N_3O_3$. Calculated: C 55.2; H 7.2%.

2-Piperidinomethyl-4,6-dimethyl-5-hydroxypyrimidine 1-Oxide (IIIb). A mixture of 0.28 g (2 mmole) of IIa, 0.2 g of dry paraformaldehyde, and 5 ml of piperidine was refluxed for 15 min, after which it was evaporated to dryness at 50°C (30 mm), and the residue was dissolved in acetone. The reaction product was isolated from the solution with a column by elution, initially with acetone—methanol and then with methanol (R_f 0.49). This procedure gave a fraction containing 0.31 g (66%) of a substance with mp 153-155°C (from benzene). PMR spectrum: 2.31 (3H, s, 6-CH_3), 2.42 (3H, s, 4-CH_3), 1.52 (6H, m, β, γ-CH_2), 2.50 (4H, m, α-CH_2), and 3.60 ppm (2H, s, CH_2). Found: C 60.6; H 8.2%. $C_{12}H_{19}N_3O_2$. Calculated: C 60.7; H 8.1%.

2-(N-Methylene-2-carboxymethylpyrrolidino)-4,6-dimethyl-5-hydroxypyrimidine 1-Oxide (IIIc). A 0.4-g (2.4 mmole) sample of N-methoxymethyl-L-proline methyl ester [17] was added to 0.28 g (2 mmole) of IIa in 10 ml of dry dioxane, and the mixture was heated up to the boiling point and allowed to stand in air for 24 h. The precipitated crystals were removed by filtration and washed with dioxane to give 0.32 g of IIIc. The filtrates were evaporated, and the residue was separated with a column packed with silica gel by elution with acetone—methanol (R_f 0.22) to give an additional amount of the product for an overall yield of 0.43 g (82%) of a substance with mp 208-210°C (dec., from dioxane) and $[\alpha]_{436}^{20} = -9.36°$. PMR spectrum: 2.60 (3H, s, 6-CH_3), 2.64 (3H, s, 4-CH_3), 2.49 (2H, m, —CH_2—), 3.61 (2H, m, —CH_2—), 4.23 (2H, m, —CH_2—), and 4.56 ppm (2H, m, N—CH_2-pyrimidine). Found: C 59.3; H 6.6%. $C_{13}H_{19}N_3O_4$. Calculated: C 59.3; H 6.5%.

2-Dimethylaminomethyl-4,6-dimethyl-5-hydroxypyrimidine 1-Oxide (IIId). A) A solution of 1 ml of N,N,N',N'-tetramethylmethylenediamine in 5 ml of benzene was added dropwise in the course of 30 min to a refluxing suspension of 0.28 g (2 mmole) of IIa in 10 ml of benzene, after which it was refluxed for another 10 min. It was then evaporated to 5 ml, and the concentrate was allowed to stand for 12 h. The precipitated crystals were removed by filtration and washed with 1 ml of cold acetone to give 0.34 g (85%) of IIId with mp 109-111°C (from methyl ethyl ketone). PMR spectrum: 2.38 (3H, s, 6-CH_3), 2.44 (3H, s, 4-CH_3), 2.62 [6H, s, $N(CH_3)_2$], and 4.12 ppm (2H, s, —CH_2—N). Found: C 54.7; H 7.8%. $C_9H_{15}N_3O_2$. Calculated: C 54.8; H 7.7%.

B) The same substance was obtained by heating 0.42 g (3 mmole) of IIa with a mixture of 1.5 ml of a 33% aqueous solution of dimethylamine and 1.9 ml of 25% formalin at 70°C for 3 h. The mixture was then evaporated at 50°C (30 mm), and the resulting light-colored oil was triturated while heating with 3 ml of acetone. After crystallization had begun, the mixture was allowed to stand at 20°C for 1 h. The precipitate was removed by filtration and washed with 1 ml of cold acetone to give 0.37 g of 1-oxide IIId, which was identical to the previously obtained compound. The filtrates were evaporated, and the residue was separated with a column (elution with methanol) to give another 0.02 g of IIId (for an overall yield of 62%) and 0.03 g (5%) of 4-dimethylaminoethyl-5-hydroxy-6-methylpyrimidine 1-oxide (IV) with mp 145-147°C (from isopropyl alcohol). PMR spectrum: 2.37 (3H, s, 6-CH_3), 2.96 [6H, s, $(CH_3)_2$], 3.37 (4H, s, CH_2CH_2), and 8.25 ppm (1H, s, 2-H). Found: C 54.8; H 7.7%. $C_9H_{15}N_3O_2$. Calculated: C 54.8; H 7.7%.

2,6-Dimethyl-4-dimethylaminoethyl-5-hydroxypyrimidine 1-Oxide (V). A mixture of the reagents and IIb in the same ratio as in the preceding experiment (method B) was heated at 100°C for 3 h after which it was evaporated *in vacuo* to two thirds of its original volume. The precipitated starting 1-oxide (0.26 g) was removed by filtration and washed with acetone. The filtrates were evaporated to dryness, and the residue was separated with a column by

elution with methanol to give 0.07 g of the starting compound and 0.04 g (33%) of V (R_f 0.15) with mp 167-169°C (from alcohol). PMR spectrum: 2.40 (3H, s, 6-CH_3), 2.57 (3H, s, 2-CH_3), 3.00 [6H, s, $N(CH_3)_2$], and 3.45 ppm (4H, s, CH_2CH_2). Found: C 56.6; H 8.2%. $C_{10}H_{17}N_3O_2$. Calculated: C 56.8; H 8.1%.

Methylenebis[(4,6-dimethyl-5-hydroxy-2-pyrimidine) 1-Oxide] (VI). A 0.1-ml sample of triethylamine was added with stirring and refluxing to a mixture of 0.35 g (2.5 mmole) of IIa (previously ground in a mortar), 0.2 g of dry paraformaldehyde, and 0.3 ml of morpholine in 10 ml of dry chlorobenzene, after which the hot mixture was filtered, and the precipitate was washed with methanol to give 0.32 g (87%) of a product, which, after recrystallization from acetic acid, had mp > 360°C (dec. > 275°C). PMR spectrum (CF_3COOH): 2.26 (6H, s, 6,6'-CH_3), 2.42 (6H, s, 4,4'-CH_3), and 4.87 ppm (2H, s, CH_2). Found C 53.2; H 5.7; N 19.0%. $C_{13}H_{16}N_4O_4$. Calculated: C 53.4; H 5.5; N 19.2%.

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