INVESTIGATION OF SOME ELECTROPHILIC REACTIONS OF 4-PHENYL-5-HYDROXYPYRIMIDINE AND ITS 1-OXIDE

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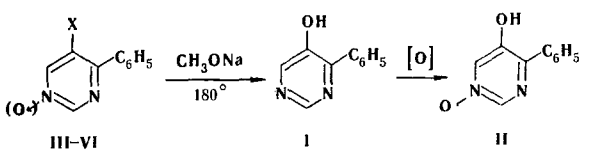
A difference in the reactivities of the 2 and 6 positions of the 5-hydroxypyrimidine ring and an effect of the N-oxide group on the direction of electrophilic-substitution reactions were demonstrated in the case of synthesized 4-phenyl-5-hydroxypyrimidine and its 1-oxide.

Previously in the case of the aminomethylation and diazo coupling of 5-hydroxypyrimidine [1] and 4,6-dimethyl-5-hydroxypyrimidine [2] we established the possibility of electrophilic substitution in various positions of the ring. This was responsible for our interest in a study of the electrophilic reactions of 4-phenyl-5-hydroxypyrimidine (I) and its 1-oxide (II) that would enable us to compare the reactivities of the ortho and para positions of the pyrimidine ring and also to ascertain the effect of phenyl and n-oxide groups on the ability of the ring to undergo electrophilic substitution (here and subsequently, the ortho and para positions of the heteroring are determined relative to the hydroxy group).

We have investigated several appraoches to the synthesis of I and II. The accessible substances for their synthesis were 5-bromo- and 5-methoxy-4-phenylpyrimidines (III, V) [3, 4] and their N-oxides (IV, VI). Hydrolytic cleavage of V with sodium methoxide at 180°C led to the production of pyrimidine I in good yield. Incomplete conversion of the starting compounds occurs when the reaction temperature is lowered, even when the reaction time is increased significantly. Oxide VI is deoxygenated at 130-140°C to give a mixture of I and V.

Positive results were not obtained when milder conditions of hydrolytic cleavage of the alkoxyaromatic derivatives by the action of trimethylchlorosilane and sodium iodide [5] were used or in the case of treatment with 30% hydrogen peroxide in alkaline solution [6] for V and VI. The starting compounds were recovered in both cases.

The most convenient method for the synthesis of hydroxypyrimidine I proved to be treatment of bromo derivative III with a solution of sodium methoxide at 180°C, in analogy with the synthesis of 3-hydroxypyridine [7]. The yield of I in this case reached 70%, and, in addition, the formation of 4-phenylpyrimidine (VII) was observed. The amount of the latter ranged from a few percent to 60-70%, depending on the concentrations of sodium methoxide and starting pyrimidine III. The dehalogenation of pyrimidine derivatives under the indicated conditions has not been reported. At the same time, data regarding the dehalogenation of aromatic compounds by the action of sodium methoxide in methanol at high temperatures are available [8, 9]; Zoltewicz and Sale [8] and Bunnett and Wamser [9] explained these results by the possibility of the occurrence of radical processes.



III, IV X=Br; V, VI X=OCH_3

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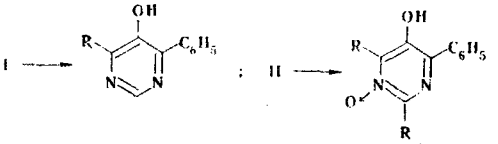
In addition to signals of aromatic protons, the PMR spectrum of I (in $CDCl_3$) contains signals at 8.70 and 8.43 ppm (2-H and 6-H). An absorption band at 3570 cm^{-1} (free OH) is observed in the IR spectrum recorded in CCl_4, whereas a broad band at 1800-2700 cm^{-1}, which indicates a strong intermolecular hydrogen bond, is observed in the IR spectrum of a KBr pellet of this compound.

Inasmuch as it was not possible to synthesize II from the corresponding 5-bromo and 5-methoxy derivatives IV and VI because of deoxygenation at high temperatures, it was obtained by oxidation of pyrimidine I with peraromatic acids. The structure of II follows unambiguously from the difference in its chromatographic behavior and spectral data as compared with the isomeric 5-hydroxy-6-phenylpyrimidine 1-oxide (VIII), which was previously described in [10].

As the initial step in the investigations of the electrophilic-substitution reactions we carried out the aminomethylation and halogenation of I and II. It is known that the most reactive position in 3-hydroxypyridine, of which 5-hydroxypyrimidine is a heteroanalog, is the 2 position of the pyridine ring (the ortho position relative to the hydroxy group and the nitrogen atom of the heteroring). If this position is occupied, as, for example, in 2-phenyl-3-hydroxypyridine, substitution is directed to the para position and then to the other ortho position [11].

The aminomethylation of I and II was carried out in both aqueous media by the action of a secondary amine and formalin and in benzene or chlorobenzene by the action of a mixture of paraformaldehyde and a secondary amine in the presence of triethylamine. As we assumed, the aminomethylation of pyrimidine I takes place in the ortho position of the ring, which is apparent from the disappearance of the 6-H signal in the PMR spectrum of product IX; in addition, signals of CH_2 groups and of the aliphatic part of the secondary amine used in the reaction appear in the spectrum. Attempts to achieve aminomethylation in the 2 position by increasing the reaction time or by the use of more severe conditions, as well as the use of large excess amounts of the reagents, were unsuccessful. These results constitute evidence for the lower reactivity of I as compared with 2-phenyl-3-hydroxypyridine, which undergoes aminomethylation at lower temperatures, whereas it forms Mannich bis bases readily in the presence of excess amounts of the aminomethylating agents [11].



IXa,b, X XIa,c,d

X R=I; IX, XI a R= morpholinomethyl; b R= piperidinomethyl; c R= diethylaminomethyl; d R= dimethylaminomethyl

The introduction of an N-oxide group significantly increases the reactivity of 5-hydroxypyrimidine, and II gives Mannich bis bases (XIa-d) under similar conditions and even at lower temperatures. An attempt to obtain a monosubstitution product under milder conditions or by the addition of the calculated amount of aminomethylating agent led to the production of a mixture of starting II, a bis base, and a very small amount of a monosubstitution product (XII); this was confirmed by chromatographic separation of the reaction products and their identification by thin-layer chromatography (TLC) and the PMR spectra, in which disappearance of the signal of one of the protons of the pyrimidine ring is observed. However, additional studies are required for the completely reliable establishment of the site of introduction of the substituent.

We were able to accomplish halogenation in the case of iodination of pyrimidine I in ammonium hydroxide, in which 4-iodo-5-hydroxy-6-phenylpyrimidine (X) was obtained in good yield. No reaction with N-oxide II was observed with N-oxide II. This result, particularly in the light of the increase in the reactivity of the N-oxide in aminomethylation , can be explained by steric interaction of the hydroxy group and the p electrons of the oxide oxygen atom with the bulky electron shell of the attacking particle during iodination, which makes electrophilic substitution impossible. The iodination of 3-hydroxypyridine 1-oxide under similar conditions [12] leads to the formation of 4,6-diiodo-3-hydroxypyridine 1-oxide as the only product, i.e., the 2 position, which is the most active position in aminomethylation, does not undergo substitution under the selected conditions.

Thus our studies made it possible to find suitable conditions for the synthesis of 4-phenyl-5-hydroxypyrimidine and its oxide. A study of the electrophilic substitution of I and II made it possible to ascertain the lower activity of 5-hydroxypyrimidines as compared with the analogous derivatives of the 3-hydroxypyridine series.

EXPERIMENTAL

The PMR spectra of 8-10% solutions of the compounds were recorded with HA-100 and A 56/60 spectrometers with hexamethyldisiloxane as the standard. Column chromatography was carried out on 40/100 μ silica gel (Czechoslovakian SSR); TLC was carried out on Silufol UV-254 plates.

5-Bromo-4-phenylpyrimidine (III). A 16-ml sample of 40% HBr was added with stirring and cooling (0-5°C) to a solution of 8 g (0.051 mole) of 4-phenylpyrimidine in 80 ml of H_2SO_4, after which a cold saturated solution of 10.4 g (0.15 mole) of sodium nitrite was added dropwise at 0°C. Another 48 ml of HBr was added at the same temperature, the mixture was stirred for 1 h, and the temperature was then brought up to room temperature. The mixture was cooled again, 100 ml of chloroform was added, and the mixture was neutralized with 20% NaOH. The organic layer was washed with water and dried with anhydrous $MgSO_4$, the solvent was evaporated, and the solid residue was washed on the filter with ether to give 5.2 g of 5-bromo-4-phenylpyrimidine with mp 93-94°C (mp 95-97°C [3]). The ether mother liquor was evaporated, and the residue was purified with a column packed with silica gel by elution with chloroform to give an additional 0.8 g of the product for an overall yield of 6.0 g (50%).

5-Hydroxy-4-phenylpyrimidine (I). A mixture of 8 g (0.034 mole) of III and 9.2 g (0.170 mole) of sodium methoxide in 300 ml of methanol was heated in an autoclave at 180°C for 8 h, after which it was poured into 200 ml of water, and the aqueous mixture was neutralized with 10% HCl and extracted with chloroform in an apparatus for continuous extraction for 10 h. The extract was dried with $MgSO_4$ and evaporated, and the residue was separated with a column packed with silica gel by successive elution with chloroform and chloroform–acetone (9:1 and 4:1) to give 0.5 g (10%) of 4-phenylpyrimidine and 4.2 g (72%) of 5-hydroxy-4-phenylpyrimidine with mp 191-192°C (from alcohol). PMR spectrum (d_6-DMSO + $CDCl_3$): 7.30-7.63 (3H, m, Ar), 8.17-8.37 (2H, m, Ar), 8.43 (1H, s, 6-H), and 8.70 ppm (1H, s, 2-H). IR spectrum (CCl_4): 3570 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 202 (4.28), 245 (3.92), and 303 nm (4.11). Found: C 69.9; H 4.7; N 16.4%; M^+ 172. $C_{10}H_8N_2O$. Calculated: C 69.8; H 4.7; N 16.3%; M 172.

4-Phenyl-5-hydroxypyrimidine 1-Oxide (II). A 6.0-g sample of 80% m-chloroperbenzoic acid was added to a solution of 2.5 g (14.5 mmole) of 4-phenyl-5-hydroxypyrimidine in 70 ml of acetone, and the mixture was allowed to stand at 20°C for 3 days. The precipitate was removed by filtration to give 1.0 g (37%) of pale-pink crystals with mp 243-245°C (dec., from alcohol). PMR spectrum (d_6-DMSO): 7.27-7.63 (3H, m, Ar), 7.90-8.13 (2H, dd, J = 2.5 and 6.0 Hz, Ar), 8.13 (1H, d, J = 1.8 Hz, 6-H), and 8.67 ppm (1H, d, 2-H). UV spectrum, λ_{max} (log ε): 204 (4.14), 240 (4.12), 280 (3.92), and 358 nm (3.74). Found: C 58.0; H 4.8; N 13.5%. $C_{10}H_8N_2O_2 \cdot H_2O$. Calculated: C 58.2; H 4.9; N 13.6%.

4-Iodo-5-hydroxy-6-phenylpyrimidine (X). A 1.72-g (10 mmole) sample of I was dissolved in 15 ml of 10% ammonium hydroxide, a solution of 3.0 g (11.5 mmole) of iodine in 35 ml of water containing 4 g of KI was added at 45°C, and the mixture was stirred at this temperature for 4 h. The mixture was cooled to 20°C, the excess iodine was removed with a solution of sodium bisulfite, and the mixture was evaporated *in vacuo* to one third of its original volume. The reaction product was precipitated by adding acetic acid with stirring. The precipitate was removed by filtration, washed with water, and dried to give 2.14 g (72%) of X with mp 104-106°C (from aqueous alcohol). PMR spectrum (CD_3OD): 7.40 (1H, s, 2-H), 7.05 (m, 2H, Ph), and 6.60 ppm (3H, m, Ph). Found: C 40.4; H 2.8; N 9.7%. $C_{10}H_7IN_2O$. Calculated %: C 40.2; H 2.7; N 9.5%.

4-Morpholinomethyl-5-hydroxy-6-phenylpyrimidine (IXa). A) A 0.1-ml sample of morpholine, 0.05 ml of triethylamine, and 0.05 g of dry paraformaldehyde were added with stirring to a suspension of 0.17 g (1 mmole) of I in 5 ml of chlorobenzene, and the mixture was refluxed for 10 min. The solvent was evaporated *in vacuo*, ethyl acetate was added to the residue, and the resulting solution was filtered through a layer of silica gel at 40-50°C. The filtrate was evaporated to dryness to give 0.18 g (66%) of IXa with mp 110-112°C (from

hexane). PMR spectrum (d_6-DMSO): 8.85 (1H, s, 2-H), 8.39 (2H, m, Ph), 7.67 (3H, m, Ph), 4.19 (2H, s, CH_2), 3.88 (4H, m, CH_2—N—CH_2), and 2.80 ppm (4H, m, CH_2—O—CH_2). Found: C 66.5; H 6.3; N 15.6%. $C_{15}H_{17}N_3O_2$. Calculated: C 66.4; H 6.3; N 15.5%.

B) A mixture of 0.1 g of I, 1.0 ml of 35% formalin, and 0.2 ml of morpholine was heated with stirring at 100°C for 2 h, after which it was allowed to stand at room temperature for 12 h. The precipitated colorless crystals were removed by filtration, washed with water, dried, and recrystallized from hexane to give 0.03 g (19%) of a compound, which, according to its melting point and TLC data, was identical to IXa.

4-Piperidinomethyl-5-hydroxy-6-phenylpyrimidine (IXb). This compound was obtained by the same method by the addition of piperidine instead of morpholine. Workup gave 0.19 g (68%) of a product with mp 74-76°C. PMR spectrum: 8.80 (1H, s, 2-H), 8.58 (2H, m, Ph), 7.67 (3H, m, Ph), 4.09 (2H, s, CH_2), 2.86 (4H, m, CH_2—N—CH_2), and 1.89 ppm (6H, m, $3CH_2$). Found: C 71.3; H 7.2; N 15.5%. $C_{16}H_{19}N_3O$. Calculated: C 71.3; H 7.1; N 16.5%. Compounds IXc, d were similarly obtained.

2,6-Bis(morpholinomethyl)-4-phenyl-5-hydroxypyrimidine 1-Oxide (Xa). A 0.1-ml sample of morpholine, 0.05 g of dry paraformaldehyde, and three drops of triethylamine were added with stirring to a suspension of ground (in a mortar) 1-oxide II [0.19 g (1 mmole)] in 5 ml of benzene, and the mixture was refluxed for 15 min, and the hot mixture was filtered. The filtrate was evaporated to dryness at 50°C (15 mm), the residue was triturated with 0.5 ml of ether, and the resulting flakes were removed by filtration and washed with ether to give 0.23 g (61%) of a product with R_f 0.15 (methanol) and mp 175-178°C (from acetone). PMR spectrum (D_2O + NaOD): 8.25 (2H, m, Ph), 7.68 (3H, m, Ph), 4.32 (2H, s, CH_2), 4.10 (4H, m, CH_2—N—CH_2), and 3.05 ppm (4H, m, CH_2—O—CH_2). Found: C 62.3; H 6.7; N 14.6%. $C_{20}H_{26}N_4O_4$. Calculated: C 62.2; H 6.8; N 14.5%.

2,6-Bis(diethylaminomethyl)-4-phenyl-5-hydroxypyrimidine 1-Oxide (XIc). This compound was obtained by the same method using diethylamine hydrochloride (0.4 g) and 0.3 ml of triethylamine. The mixture was heated to 70°C and allowed to stand for 1 h. It was then evaporated, and the residue was dissolved in methanol and separated with a column packed with silica gel by elution with methanol. The fraction containing XIc was evaporated to dryness, and the residue was triturated with 0.5 ml of alcohol saturated with HCl to give a dihydrochloride (57%) with mp 150-152°C (from methanol—acetone). PMR spectrum (D_2O): 8.10 (2H, m, Ph), 7.79 (3H, m, Ph), 4.88 (2H, s, CH_2), 3.57 [4H, q, CH_2(Et)], and 1.60 ppm [6H, t, CH_3(Et)]. Found: C 55.6; H 7.6; N 12.9%. $C_{20}H_{30}N_4O_2 \cdot 2HCl$. Calculated: C 55.7; H 7.5; N 13.0%.

2,6-Bis(dimethylaminomethyl)-4-phenyl-5-hydroxypyrimidine 1-Oxide (XId). Thoroughly ground 1-oxide II (0.19 g) was refluxed in a mixture of 3 ml of isopropyl alcohol and 1 ml of N,N,N',N'-tetramethylmethylenediamine for 30 min, after which it was evaporated at 50°C (15 mm), and the residue was triturated with 0.5 ml of dry benzene to give 0.13 g (43%) of a crystalline precipitate with mp 157-158°C (from methanol—acetone) and R_f 0.08 (methanol). PMR spectrum (D_2O): 8.03 (2H, m, Ph), 7.75 (3H, m, Ph), 4.88 (4H, s, $2CH_2$), and 3.22 and 3.15 ppm (6H + 6H, two s, CH_3—N—CH_3). Found: C 63.7; H 7.4; N 18.4%. $C_{16}H_{22}N_4O_2$. Calculated: C 63.6; H 7.3; N 18.5%.

2(6)-Dimethylaminomethyl-4-phenyl-5-hydroxypyrimidine 1-Oxide (XII). A 0.19-g sample of 1-oxide II was refluxed in 1 ml of methanol for 3 h, during which 5 ml of N,N,N',N'-tetramethylmethylenediamine was added during the first 2 h. The mixture was evaporated *in vacuo*, and the residue was dissolved in acetone, and the solution was applied to a column packed with silica gel and eluted with acetone to give 0.05 g of the starting compound. The eluent was replaced by methanol, and a fraction containing 0.11 g (61%) of XII, with mp 225-227°C (dec., from methanol) and R_f 0.22 (methanol), was obtained. PMR spectrum (d_6-DMSO): 8.51 (2H, m, Ph), 7.90 [1H, s, 6(2)-H], 7.62 (3H, m, Ph), 4.58 (2H, s, CH_2), and 2.72 ppm (6H, s, CH_3—N—CH_3). Found: C 63.9; H 6.3; N 17.3%. $C_{18}H_{15}N_3O_2$. Calculated: C 63.7; H 6.2; N 17.1%.

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ACID–BASE PROPERTIES AND STRUCTURES OF 5-HYDROXYPYRIMIDINE DERIVATIVES AND THEIR N-OXIDES

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The acid–base properties of some 5-hydroxypyrimidine derivatives and their N-oxides were investigated in comparison with the analogous 3-hydroxypyridine derivatives. It was found that 5-hydroxypyrimidines exist in the hydroxy form and are protonated at the nitrogen atom, whereas their N-oxides are protonated at the oxide oxygen atom, in contrast to the N-oxides of other diazines (pyridazine and quinoxaline). The character of the effect of ortho and para substituents (alkyl, benzyl, and phenyl) on the basicities and acidities of the indicated compounds was ascertained.

Virtually no data on the acid–base equilibria of 5-hydroxypyrimidine derivatives (I) are available; this is due to their low accessibility. At the same time, data on the acid–base transformations of 3-hydroxypyridine derivatives (II) [1-3], of which I are aza analogs, are available. In this connection, it seemed of interest to study the acidities and basicities of derivatives I and their 1-oxides (III) and to compare them with data on derivatives II.

The basicities of the selected compounds were studied in nitromethane, which is suitable for the determination of the pK_{BH^+} values of weak bases, which I and, particularly, III are, and was previously used for the investigation of derivatives II [1], pyrimidine, and 1,3,5-triazine [4]. To determine the acidities of I and III we used 50% alcohol, in which these compounds are more soluble than in water.

Before we discuss the data obtained, we must examine the tautomeric compositions and the direction of the protolytic reactions of the investigated compounds. Judging from the literature data and our data, derivatives I exist in the hydroxy form (IV) in the selected solvents. In fact, it is known that the tautomeric equilibria of I are shifted to favor the hydroxy form to a much greater degree than in the case of II (in aqueous solution the amount of the hydroxy form for 3-hydroxypyridine is ∿50%, as compared with 98% for 5-hydroxypyrimidine) [5]. The normal form of the titration curves [6] of derivatives I indicates that they are protonated at one of the nitrogen atoms (hydroxy form) rather than at the oxygen center (the zwitter-ion form). Finally, the introduction of a 5-hydroxy group has only a slight effect on the basicity of pyrimidine in nitromethane (the pK_{BH^+} of pyrimidine is

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