REACTION OF SUBSTITUTED 2- AND 4-METHYLPYRIMIDINES WITH AROMATIC CARBOXYLIC ACID CHLORIDES

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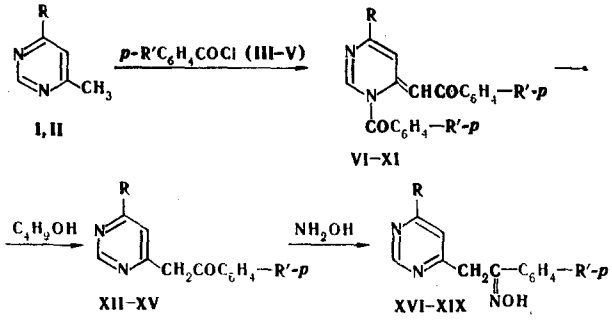
The effect of substituents in methylpyrimidines on the reaction of the methyl groups with aromatic carboxylic acid chlorides in the presence of triethylamine was studied. It is shown that, depending on the character of the substituents, the reaction with the acid chlorides takes place at the methyl groups or at the ring nitrogen atoms.

We have previously studied the reaction of methyl groups in the pyrimidine ring with aromatic carboxylic acid chlorides in the case of 4,6-dimethylpyrimidine [1, 2]. In the present research we investigated the effect of electron-donor and electron-acceptor substituents on the reactivity of methyl groups in pyrimidines in reactions with acid chlorides.

6-Substituted 4-methylpyrimidines I and II, which contain electron-donor substituents [OCH_3 and $N(CH_3)_2$], react with acid chlorides in the presence of triethylamine to give N-acyl-6-R-4-phenacylidenepyrimidines (VI-XI).



I R=OCH_3; II R=$N(CH_3)_2$; III R′=H; IV R′=Cl; V R′=OCH_3; VI, XII, XVI R=OCH_3, R′=H; VII, XIII, XVII R=OCH_3, R′=Cl; VIII R=R′=OCH_3; IX, XIV, XVIII R=$N(CH_3)_2$, R′=H; X, XV, XIX R=$N(CH_3)_2$, R′=Cl; XI R=$N(CH_3)_2$, R′=OCH_3

The N-acyl derivatives are readily hydrolyzed in aqueous butanol and give phenacylpyrimidines XII-XV. In an attempt to hydrolyze VI with 2 N NaOH we isolated a product of hydrolysis of the acyl and methoxy groups, viz., 6-hydroxy-4-phenacylpyrimidine (XX), the structure of which was proved by mass spectrometry.

The reaction of active methyl groups with acid chlorides takes place in the presence of a strong base such as triethylamine but does not occur in pyridine (pK_a 5.17). The carbanion formed as a result of deprotonation of the methyl groups undergoes electrophilic attack by acid chlorides to give phenacylpyrimidines XII-XV. The anion of one of the three possible tautomeric forms of the phenacylpyrimidines (an o-quinoid structure is indicated arbitrarily in the scheme) subsequently reacts with the acid chlorides and gives N-acylphenacylidenepyrimidines VI-XI. This is confirmed in the case of phenacylpyrimidine XIII, from which N-acyl derivative VII was obtained by reaction with acid chloride IV.

The PMR spectrum contains the signals of the proton of a methylidyne group (6.13 ppm) and an NH group (14.27 ppm), which confirms the existence of a tautomeric form. The pyrimidinylidene structure is also confirmed by data from the UV spectra, in which long-wave absorption at 334 nm is observed.

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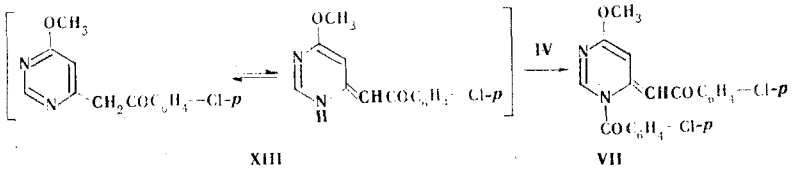


XIII VII

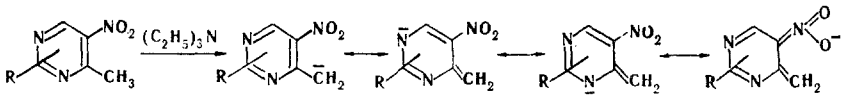
2-Methylpyrimidine reacts with benzoyl chloride only in acetonitrile to give 2-phenacylpyrimidine (XXI), from which oxime XXII was obtained.

The stronger the electron-donor substituent (for example, the dimethylamino group), the more readily the reaction of methylpyrimidines with the acid chlorides proceeds. Thus the reaction of II proceeds in benzene and even with heat evolution in acetonitrile, while I reacts only in acetonitrile.

The reaction proceeds in a different manner when a strong electron acceptor such as the nitro group is introduced in the 5 position of methylpyrimidine. Triethylamine hydrochloride and starting methylpyrimidine XXIII were isolated in quantitative yield as a result of the reaction of 5-nitro-2,6-dimethoxy-4-methylpyrimidine (XXIII) with benzoyl chloride in the presence of triethylamine under the conditions indicated above. The product in this case is apparently an N-acyl derivative, which we were unable to isolate, since it is extremely unstable as a consequence of the low basicity of XXIII and is readily hydrolyzed during isolation from the reaction mixture. The methoxy group has virtually no effect on the basicity of pyrimidine; for example, the pK_a value of pyrimidine is 1.31, while the pK_a value of 4,6-dimethoxypyrimidine is 1.49 [3].

Just as in the case of XXIII, only triethylamine hydrochloride was isolated in quantitative yield as a result of the reaction of 5-nitro-4,6-dimethoxy-2-methylpyrimidine with benzoyl chloride.

The different course of the reaction of acid chlorides with methylpyrimidines is explained by the effect of the substituents on the properties of the carbanions formed by the action of triethylamine.



The carbanions of methylpyrimidines are stabilized by the —I and —M effects of the pyrimidine ring. Sufficient electron density, which promotes electrophilic attack by acid chlorides, is retained on the carbanion in the case of electron-donor substituents, and phenacylpyrimidines are formed. Delocalization is intensified when a nitro group is present, and the electron density is shifted to the ring nitrogen atoms and the nitro group, which leads to the formation of an unstable N-acyl derivative.

Oximes XVI-XIX were obtained from phenacylpyrimidines XII-XV by reaction with hydroxylamine.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the external standard. The UV spectra of $\sim 10^{-4}$ mole/liter solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The mass spectrum was recorded with an MS-902 spectrometer at an ionization energy of 70 eV and an ionization-chamber temperature of 100°C.

N-Benzoyl-6-methoxy-4-phenacylidenepyrimidine (VI). A solution of 4.2 g (30 mmole) of benzoyl chloride in 10 ml of absolute acetonitrile was added with stirring to a solution of 1.24 g (10 mmole) of I and 3 g (30 mmole) of triethylamine in 20 ml of absolute acetonitrile, and the mixture was stirred at 0°C for 2 h. The triethylamine hydrochloride (92%) was removed by filtration, and the filtrate was evaporated *in vacuo*. The residue was washed with water and crystallized from petroleum ether (70-100°C) to give 1.4 g (41%) of VI with mp 105-106°C. UV spectrum, λ_{max} (log ε): 332 nm (4.38). PMR spectrum (CCl_4): 4.10 (s, 3H, OCH_3), 7.02 (s, 2H, CH= and 5-H), 7.70 (m, 10H, 2-C_6H_5), and 8.77 ppm (s, 1H, 2-H). Found: C 72.3; H 4.8; N 7.8%. $C_{20}H_{16}N_2O_3$. Calculated: C 72.3; H 4.9; N 8.4%.

N-(p-Chlorobenzoyl)-6-methoxy-4-(p-chlorophenacylidene)pyrimidine (VII). This compound was similarly obtained from I. The triethylamine hydrochloride was removed by filtration along with VII. The mixture was treated with water and filtered to give 3.4 g (84%) of VII with mp 145-146°C (from petroleum ether). UV spectrum, λ_{max} (log ε): 247 (4.13) and 306 nm (4.20). PMR spectrum (CCl_4): 4.06 (s, 3H, OCH_3), 6.83 (s, 2H, =CH and 5-H), 7.63 (m, 8H, 2-C_6H_4), and 8.56 ppm (s, 1H, 2-H). Found: C 59.8; H 3.4; Cl 17.6; N 6.3%. $C_{20}H_{14}Cl_2N_2O_3$. Calculated: C 59.8; H 3.5; Cl 17.7; N 6.9%.

N-Anisoyl-6-methoxy-4-(p-methoxyphenacylidene)pyrimidine (VIII). This compound was obtained from I by the method used to prepare VI. The reaction product was chromatographed with a column filled with activity II Al_2O_3 by elution with benzene–methanol (10:1). Workup gave 0.4 g (10%) of a product with mp 124-124.5°C. Found: C 66.9; H 5.1; N 7.1%. $C_{22}H_{18}N_2O_5$. Calculated: C 67.3; H 5.1; N 7.1%.

N-Benzoyl-6-dimethylamino-4-phenacylidenepyrimidine (IX). This compound was similarly obtained from II in absolute benzene by refluxing. The triethylamine hydrochloride was removed by filtration, and the filtrate was evaporated *in vacuo*. The residue was triturated with ether to give 2.5 g (66%) of the hydrochloride of IX with mp 222-226°C (from alcohol). Found: C 64.8; H 5.2; Cl 9.4; N 10.9%. $C_{21}H_{19}N_3O_2 \cdot HCl$. Calculated: C 65.6; H 5.2; Cl 9.4; N 10.9%.

A 0.8-g (2 mmole) sample of the hydrochloride of IX was treated with 2 N NaOH, and the suspension was extracted with ether. The extract was dried with $MgSO_4$ and evaporated *in vacuo*, and the residue was crystallized from petroleum ether (70-100°C) to give 0.4 g (55%) of IX with mp 118-120°C. Found: C 73.3; H 5.5; N 12.1%. $C_{21}H_{19}N_3O_2$. Calculated: C 73.0; H 5.5; N 12.1%.

N-(p-Chlorobenzoyl)-6-dimethylamino-4-(p-chlorophenacylidene)pyrimidine (X). This compound was similarly obtained from II in absolute benzene at 20°C. The triethylamine hydrochloride and reaction product X were removed by filtration and treated with water to give 1.4 g (34%) of ketone X with mp 171-172°C, which was purified by reprecipitation from chloroform–ether (1:1) by the addition of petroleum ether. PMR spectrum ($CDCl_3$): 3.30 [s, 6H, $N(CH_3)_2$], 6.92 (s, 1H, 5-H), 7.1 (s, 1H, =CH), 7.5 (m, 8H, 2-C_6H_4), and 8.73 ppm (s, 1H, 2-H). Found: C 61.5; H 4.1; Cl 16.5; N 10.0%. $C_{21}H_{17}Cl_2N_3O_2$. Calculated: C 60.9; H 4.1; Cl 17.1; N 10.1%.

N-Anisoyl-6-dimethylamino-4-(p-methoxyphenacylidene)pyrimidine (XI). This compound was similarly obtained from II in absolute benzene at 0°C. Workup gave 0.3 g (9%) of XI with mp 135-136°C (from petroleum ether). Found: C 67.8; H 5.7; N 10.1%. $C_{23}H_{24}N_3O_2$. Calculated: C 67.9; H 5.9; N 10.4%.

6-Methoxy-4-phenacylpyrimidine (XII). A 3.3-g (10 mmole) sample of VI was refluxed in 25 ml of aqueous butanol for 4 h, after which the mixture was cooled, and the precipitate was removed by filtration to give 1.2 g (52%) of a product with mp 91-92°C. UV spectrum, λ_{max} (log ε): 246 (4.09) and 334 nm (4.09). Found: C 68.4; H 5.2; N 12.1%. $C_{13}H_{12}N_2O_2$. Calculated: C 68.4; H 5.3; N 12.3%.

6-Methoxy-4-(p-chlorophenacyl)pyrimidine (XIII). This compound was similarly obtained. Workup gave a substance with mp 115-116°C in 64% yield. UV spectrum, λ_{max} (log ε): 252 (4.15) and 334 nm (4.0). PMR spectrum (CCl_4): 4.30 (s, 3H, OCH_3), 6.13 (s, 1H, =CH), 6.60 (s, 1H, 5-H), 7.83 (m, 4H, C_6H_4), 8.83 (s, 1H, 2-H), and 14.27 ppm (s, 1H, NH). Found: C 58.7; H 4.4; Cl 13.5; N 10.6%. $C_{13}H_{11}ClN_2O_2$. Calculated: C 59.4; H 4.2; Cl 13.5; N 10.7%.

6-Dimethylamino-4-phenacylpyrimidine (XIV). This compound was similarly obtained. After the heating period, the butanol was evaporated *in vacuo*, and the residue was crystallized from petroleum ether (70-100°C) to give a product with mp 112-114°C in 83% yield. UV spectrum, λ_{max} (log ε): 250 nm (4.25). PMR spectrum (CCl_4): 3.46 [s, 6H, $N(CH_3)_2$], 6.10 (s, 1H, =CH), 6.30 (s, 1H, 5-H), 7.66 (m, 5H, C_6H_5), and 8.63 ppm (s, 1H, 2-H). Found: C 69.9; H 6.3; N 17.4%. $C_{14}H_{15}N_3O$. Calculated: C 69.7; H 6.3; N 17.4%.

6-Dimethylamino-4-(p-chlorophenacyl)pyrimidine (XV). This compound was obtained by refluxing X in methanol for 5 min. Workup gave a product with mp 134-136°C (from petroleum ether) in 74% yield. UV spectrum, λ_{max} (log ε): 252 (4.88) and 360 nm (4.68). PMR spectrum (CCl_4): 3.40 [s, 6H, $H(CH_3)_2$], 6.03 (s, 1H, =CH), 6.23 (s, 1H, 5-H), 7.80 (m, 4H, C_6H_4), and 8.60 ppm (s, 1H, 2-H). Found: C 61.1; H 5.1; Cl 12.9; N 15.2%. $C_{14}H_{14}ClN_3O$. Calculated: C 60.9; H 5.1; Cl 12.8; N 15.2%.

6-Methoxy-4-phenacylpyrimidine Oxime (XVI). A yellow suspension of 0.23 g (1 mmole) of XII and 0.14 g (2 mmole) of hydroxylamine hydrochloride in 7 ml of absolute alcohol and 7 ml of absolute pyridine was allowed to stand for 24 h, during which the solid material dissolved, and the solution became colorless. The solution was evaporated *in vacuo*, water was added to the residue, and the mixture was filtered to give 0.2 g (87%) of a product with mp 119-120°C. Found: C 64.7; H 5.4; N 17.1%. $C_{13}H_{13}N_3O_2$. Calculated: C 64.2; H 5.4; N 17.3%.

6-Methoxy-4-(p-chlorophenacyl)pyrimidine Oxime (XVII). This compound was obtained in the same way as oxime XVI. Workup gave 0.24 g (85%) of a product with mp 117-118°C (from petroleum ether). Found: C 56.4; H 4.9; Cl 12.8; N 15.9%. $C_{13}H_{12}ClN_3O_2$. Calculated: C 56.2; H 4.4; Cl 12.8; N 15.1%.

6-Dimethylamino-4-phenacylpyrimidine Oxime (XVIII). This compound was obtained in the same way as oxime XVI. Workup gave a product with mp 176-177°C. Found: C 65.1; H 6.3; N 21.7%. $C_{14}H_{16}N_4O$. Calculated: C 65.0; H 6.3; N 21.9%.

6-Dimethylamino-4-(p-chlorophenacyl)pyrimidine Oxime (XIX). This compound was obtained in the same way as oxime XVI. Workup gave 0.25 g (80%) of a product with mp 193-196°C. Found: C 57.4; H 5.2; N 19.2%. $C_{14}H_{15}ClN_4O$. Calculated: C 57.8; H 5.2; N 19.3%.

6-Hydroxy-4-phenacylpyrimidine (XX). A 0.7-g (2 mmole) sample of VI was treated with 2 N NaOH at 20°C. The precipitate was removed by filtration to give 0.2 g (42%) of XX with mp 251-254°C (from ethanol). Mass spectrum: 214 (M^+), 197 $(M - OH)^+$, 186 $(M - CO)^+$, 137 $(M - C_6H_5)^+$, 109 $(M - C_6H_5CO)^+$, 105 ($C_6H_5CO^+$), and 77 ($C_6H_5^+$). Found: C 67.6; H 5.2; N 12.9%. $C_{12}H_{10}N_2O_2$. Calculated: C 67.3; H 4.7; N 13.1%.

Reaction of 6-Methoxy-4-(p-chlorophenacyl)pyrimidine (XIII) with Acid Chloride IV. A solution of 0.35 g (2 mmole) of acid chloride IV in 5 ml of absolute benzene was added with stirring at 20°C to a solution of 0.5 g (2 mmole) of XIII and 0.16 g (2 mmole) of pyridine in 10 ml of absolute benzene, and the mixture was allowed to stand overnight. The pyridine hydrochloride was removed by filtration, the filtrate was evaporated *in vacuo*, and the residue was triturated with petroleum ether to give 0.8 g (98%) of VII with mp 145-146°C. No melting point depression was observed for a mixture of this product with a sample of VII obtained from I.

2-Phenacylpyrimidine (XXI). A solution of 2.8 g (20 mmole) of III in 10 ml of absolute acetonitrile was added with stirring at 0°C to a solution of 0.94 g (10 mmole) of 2-methylpyrimidine and 2 g (20 mmole) of triethylamine in 20 ml of absolute acetonitrile, and the mixture was allowed to stand overnight at 0°C. The triethylamine hydrochloride (73%) was removed by filtration. The filtrate was evaporated *in vacuo*, and the residue was treated with sodium carbonate solution. The mixture was extracted with ether, and the extract was dried with $MgSO_4$. The ether was removed by distillation, and the residue was dissolved in ethyl acetate and precipitated with petroleum ether to give 0.4 g (19%) of a substance with mp 142-143°C (from petroleum ether). Found: C 72.8; H 5.1; N 13.8%. $C_{12}H_{10}N_2O$. Calculated: C 72.7; H 5.1; N 14.1%.

2-Phenacylpyrimidine Oxime (XXII). This compound was obtained in the same way as oxime XVI. Workup gave a product with mp 164-166°C [from methanol–water (5:3)] in 85% yield. Found: C 67.6; H 5.2%. $C_{12}H_{11}N_3O$. Calculated: C 67.6; H 5.2%.

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