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4-Arylamino-2-(2-acetoxyethyl)amino-6-methylpyrimidines: Synthesis, Deacetylation, and Biological Activity

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Abstract — The reaction of 2-(2-acetoxyethyl)amino-4-chloro-6-methylpyrimidine with aromatic amines leads to a series of 4-arylamino-2-(2-acetoxyethyl)amino-6-methylpyrimidines. Deacetylation of these compounds proceeds in both acidic and basic media. Most of the arylaminopyrimides obtained exhibit a pronounced antituberculous effect.

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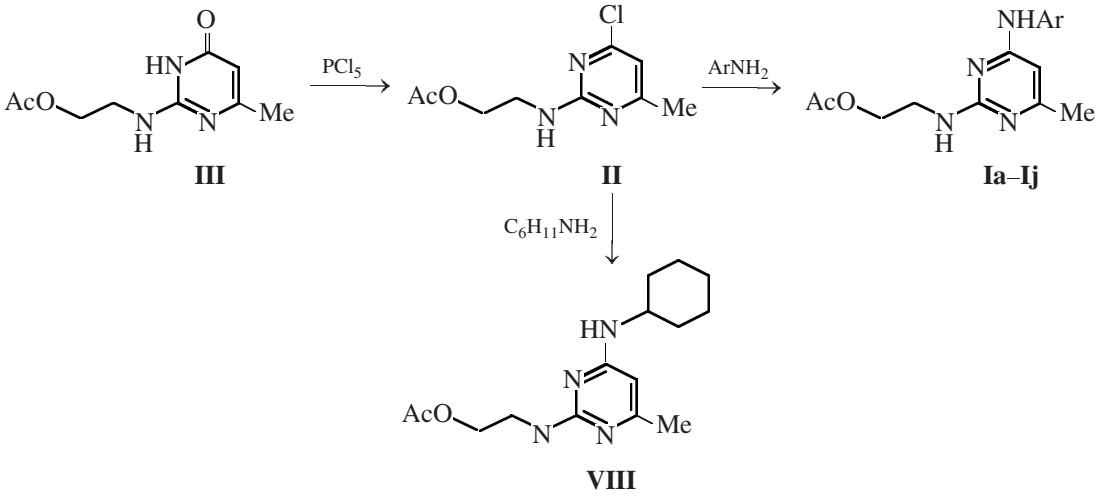
A convenient synthetic approach to new biologically active compounds of the pyrimidine series is provided by nucleophilic substitution of halogen atoms or other easily leaving groups in even positions of the ring by pharmacophoric groups. The aim of this work was to synthesize 4-arylamino-2-(2-acetoxyethyl)-amino-6-methylpyrimidines **Ia**–**Ij** by amination of 2-(2-acetoxyethyl)amino-6-methylpyrimidin-4(3*H*)-one (**III**) with aromatic amines, to study deacetylation of the target compounds under various conditions, and to assess their biological activity. According to published data [1], the target compounds would be expected to exhibit antibacterial properties.

We compared exchange chlorination of 2-(2-acetoxyethyl)amino-6-methyl-pyrimidin-4(3*H*)-one (**III**) with phosphorus oxytrichloride [2] and pentachloride [3] and gave preference to latter method as providing stable yields of 60–70% and high purity of chloride **II**. Heating of an equimolar mixture of acetate **III** and phosphorus pentachloride at 100–110°C for no longer than 15 min and subsequent decomposition of the reaction mixture with ice and its neutralization with aqueous ammonium hydroxide at 0°C (external cooling) should be considered close to optimal conditions. When no cooling is applied, strong heat release takes place, which reduces the yield of chloride **II** to 35%.



The decreased reactivity of the halogen atom in 2-amino-4-chloropyrimidines [4] prompted us to carry out amination of compound **II** with aromatic amines under rigid conditions at a 1 : 2 substrate : reagent ratio (method *a*). However, under such conditions arylaminopyrimidines **Ia**–**Id** could not be isolated in reasonable yields and chromatographic purity due to significant tarring of the reaction mixture. To go

Table 1. Yields, melting points, and TLC and elemental analysis data of 4-arylamino-2-(2-acetoxyethyl)amino-6-methylpyrimidines **Ia**–**Ij**

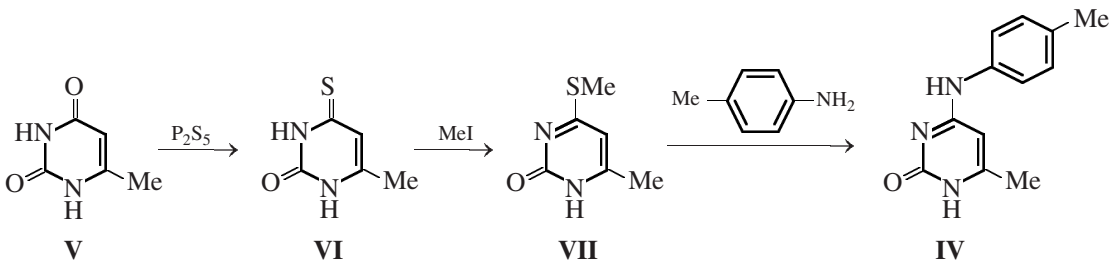
Comp. no.	Ar	Method of synthesis	Yield, %[a]	mp, °C[b]	R_f	Found, %			Formula	Calculated, %		
						C	H	N		C	H	N
Ia	Ph	*b*	66	218	0.81	55.50	5.92	17.05	$C_{15}H_{18}N_4O_2 \cdot HCl$	55.76	5.89	17.35
Ib	3-MeC_6H_4	*b*	29	202	0.80	57.19	6.34	16.57	$C_{16}H_{20}N_4O_2 \cdot HCl$	57.00	6.23	16.63
Ic	4-MeC_6H_4	*b*	61	206	0.82	57.22	6.46	16.73	$C_{16}H_{20}N_4O_2 \cdot HCl$	57.00	6.23	16.63
Id	4-$MeOC_6H_4$	*b*	26	193	0.75	55.03	6.43	15.87	$C_{16}H_{20}N_4O_3 \cdot HCl$	54.42	5.95	15.87
Ie	4-FC_6H_4	*a*	41	224	0.77	53.18	5.62	17.08	$C_{15}H_{17}FN_4O_2 \cdot HCl$	52.82	5.28	16.43
If	3-ClC_6H_4	*a*	53	222	0.76	50.76	5.27	15.37	$C_{15}H_{17}ClN_4O_2 \cdot HCl$	50.39	5.04	15.68
Ig	4-ClC_6H_4	*a*	44	226	0.82	50.32	5.31	15.51	$C_{15}H_{17}ClN_4O_2 \cdot HCl$	50.39	5.04	15.68
Ih	3-BrC_6H_4	*a*	65	209	0.81	44.64	4.49	13.48	$C_{15}H_{17}BrN_4O_2 \cdot HCl$	44.81	4.48	13.95
Ii	4-BrC_6H_4	*a*	46	222	0.82	44.72	4.32	13.78	$C_{15}H_{17}BrN_4O_2 \cdot HCl$	44.81	4.48	13.95
Ij	4-IC_6H_4	*a*	35	220	0.82	40.14	4.35	12.44	$C_{15}H_{17}IN_4O_2 \cdot HCl$	40.11	4.01	12.48

[a] Yields of hydrochlorides are given. [b] The products all, except for **Id**, melt with decomposition. [c] Aqueous ethanol solutions of all the compounds give positive tests for the chloride ion with aqueous solution of silver nitrate.

around these drawbacks, we treated chloride **II** with equimolar amounts of phenyl-, 3- and 4-methylphenyl-, and 4-methoxyphenylamines (method *b*). As a result, the yields of arylaminopyrimidines **Ia**–**Id** could be improved by 10–30%, and the products were chromatographically pure after single crystallization. Physicochemical characteristics of compounds **Ia**–**Ij** synthesized by methods *a* or *b* and isolated as hydrochlorides are listed in Table 1.

The structure of compounds **Ia**–**Ij** was confirmed by the ^1H NMR spectra which contain characteristic multiplets of aromatic ring protons at δ 6.8–8.00 ppm, as well as broadened singlets of protons of the amino group at the pyrimidine C^4 atom near δ 10.5 ppm and of the proton at the quaternary nitrogen atom of the ring near δ 13 ppm. Spectral parameters of compounds **Ia**–**Ij** are listed in Table 2.

Arylaminopyrimidines **Ia**–**Ij** were isolated as hydrochlorides. It was important to find out their protonation site. According to [5], 2,4-diaminopyrimidines are quaternized by the most basic nitrogen atom in the 1 position of the ring. To reveal the situation in the target compounds, we compared the UV spectra of 2-(2-acetoxyethyl)amino-6-methyl-4-(4-methylphenyl)aminopyrimidine (**Ic**) and the neutral form of the model compound, 6-methyl-4-(4-methylphenyl)-aminopyrimidin-2(1*H*)-one (**IV**). The spectra proved to be similar to each other in the long-wave range (see figure), implying that compound **Ic** is protonated by N^1 [6]. Substituted cytosine **IV** was synthesized by stepwise modification of the structure of 6-methylpyrimidine-2,4(1*H*,3*H*)-dione (**V**). Sulfurization of diketone **V** with phosphorus pentasulfide leads to 6-methyl-4-thioxo-3,4-dihydropyrimidin-2(1*H*)-one (**VI**). Its S-methylation with methyl iodide gives 6-methyl-4-(methylsulfanyl)pyrimidin-2(1*H*)-one (**VII**). Amination of thioether **VII** with (4-methylphenyl)amine under rigid conditions gave model compound **IV**.



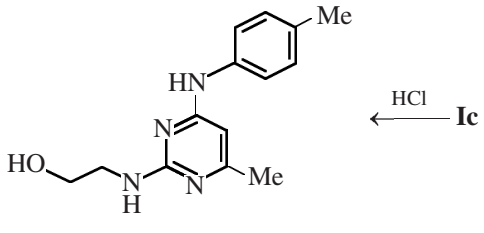
V **VI** **VII** **IV**

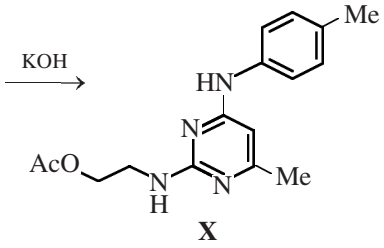
Table 2. ^{1}H NMR spectral parameters of 4-arylamino-2-(2-acetoxyethyl)amino-6-methylpyrimidines **Ia**–**Ij**

Comp. no.	Chemical shifts of protons, δ, ppm [a]								
	Ac	Me	CH_2	CH_2	CH	N^2H	N^4H	Ar	N^+H
Ia	1.99	2.32	3.65	4.18	6.25	8.14	10.80	7.12–7.69	13.28
Ib	1.98	2.31	3.65	4.18	6.23	8.11	10.71	6.94–7.55	13.21
Ic	2.00	2.31	3.64	4.18	6.22	8.16	10.73	7.11–7.56	13.29
Id	2.00	2.31	3.64	4.17	6.17	8.12	10.67	6.86–7.58	13.18
Ie	1.98	2.31	3.63	4.16	6.23	8.11	10.93	7.13–7.71	13.22
If	1.99	2.33	3.66	4.18	6.27	8.14	11.05	7.13–7.92	13.32
Ig	1.99	2.33	3.64	4.17	6.23	8.11	10.90	7.35–7.71	13.23
Ih	2.02	2.35	3.67	4.20	6.29	8.25	11.05	7.26–7.63	13.46
Ii	1.99	2.32	3.64	4.18	6.27	8.15	11.03	7.48–7.68	13.28
Ij	2.01	2.33	3.66	4.18	6.26	8.21	10.93	7.55–7.64	13.42

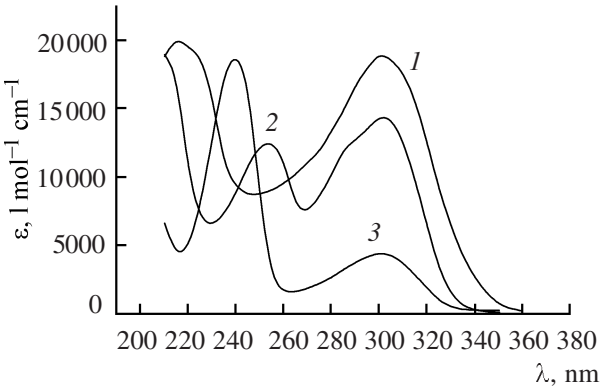
[a] The integral intensities of signals are consistent with the number of protons in the corresponding group.

The strong absorption band near 300 nm in the UV spectra of arylaminopyrimidines **Ia**–**Ij** arises mainly from charge-transfer processes in the arylamidine fragment, and, to a lower extent, from $n \rightarrow \pi^*$ transitions in the alkylamidine fragment. These assignments follow from published data [7], as well as from the low molar absorption coefficient of the long-wave band in the spectrum of 2-(2-acetoxyethyl)amino-4-cyclohexylamino-6-methylpyrimidine (**VIII**) (see figure) we synthesized by the reaction of equimolar amounts of chloride **II** and cyclohexylamine. The absence in the UV spectra of compounds **Ia**–**Ij** of absorption bands in the range 230–260 nm related to π–π* transitions in the pyrimidine and benzene rings suggests that the chromophores are incorporated in a common conjugation system.





Deacetylation of arylaminopyrimidines **Ia**–**Ij** was studied on an example of compound **Ic**. The reaction was found to proceed under the action of both acids and bases. Treatment of arylaminopyrimidine **Ic** with HCl yields 2-(2-hydroxyethyl)amino-6-methyl-4-(4-methylphenyl)aminopyrimidine (**IX**) as hydrochloride. The ^{1}H NMR spectrum of aminoethanol **IX** contains no acetyl proton signal at 1.9 ppm but contains a broadened signal of the hydroxyl proton at 4.7 ppm. In going from acidic to basic media, some interesting aspects of the reaction pathway are observed. Treatment of compound **Ic** with aqueous KOH results exclusively in dehydrochlorination, while the acetoxy group remains intact. In the ^{1}H NMR spectrum of the resulting free base 2-(2-acetoxyethyl)amino-6-methyl-4-(4-methylphenyl)aminopyrimidine (**X**), no broadened singlet of the proton at the quaternary nitrogen atom at 13.3 ppm is observed, but a signal of acetyl protons is present in the same region, like in the



UV spectra of (*1*) 2-(2-acetoxyethyl)amino-6-methyl-4-(4-methylphenyl)aminopyrimidine (**Ic**), (*2*) 6-methyl-4-(methylphenyl)aminopyrimidin-2-(1*H*)-one (**IV**), and (*3*) 2-(2-acetoxyethyl)amino-4-cyclohexylamino-6-methylpyrimidine (**VIII**).

spectrum of compound **Ic**. The reason of such behavior of arylaminopyrimidine **Ic** in aqueous alkaline solution lies in the poor solubility of its dehydrochlorination product, acetylaminoethanol **X**, in water. To provide homogeneous reaction, we carried out deacetylation of arylaminopyrimidine **Ic** with KOH in aqueous ethanol. But it occured that target aminoethanol **IX** is difficult to isolate as the free base. Therefore, we treated of the reaction product with picric acid to obtain compound **IX** picrate. The ^{1}H NMR spectrum of this compound shows a broadened singlet of hydroxyl proton at 4.8 ppm, and the integral intensity of aromatic proton signals is 6 units.

Biological screening of arylaminopyrimidines **Ia**–**Ij** in vitro showed that some of them exhibit a weak antibacterial activity with respect to *Staphylococcus aureus*, while most compounds exhibit a pronounced antituberculous activity in the concentration range 0.01–0.1 g l^{-1}. Compounds **Ih, Ij** proved to be most active. They inhibited the reproduction of *Mycobactericum smegmatis* by 100% in the concentration 0.0125 g l^{-1}. Considering that chloride **II** and diamine **VIII** do not exhibit antituberculous properties, we can suggest that the activity of arylaminopyrimidines **Ia**–**Ij** with respect to the above-mentioned strain is caused by the presence of the pharmacophoric aryl fragment in their structure.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WM-400 spectrometer (400.13 MHz) in DMSO-d_6 against residual DMSO protons. The UV spectra were recorded on an SF-26 spectrometer in ethanol ($c \sim 1 \times 10^{-4}$ M). The purity of the compounds was controlled by TLC on Silufol UV-254 plates, eluent *n*-butanol–acetic acid–water (1 : 1 : 1), development under UV light. Elemental analysis was carried out on a Hewlett-Packard B-185 analyzer.

2-(2-Acetoxyethyl)amino-4-chloro-6-methylpyrimidine (**II**) and 2-(2-acetoxyethyl)amino-6-methylpyrimidin-4(3*H*)-one (**III**) were prepared by the procedures in [3] and [2], respectively. 6-Methylpyrimidin-2,4-(1*H*, 3*H*)-dione **V** was synthesized by the procedure in [8], and 6-methyl-4-thioxo-3,4-dihydropyrimidin-2(1*H*)-one (**VI**) was obtained by the procedure in [9]. The solvents used were dried by conventional procedures [10].

4-Arylamino-2-(2-acetoxyethyl)amino-6-methylpyrimidines Ia-Ij. *a*. A mixture of 0.0022 mol of chloride **II** and 0.0044 mol of arylamine was heated for 1–2 h (TLC control) at 120°C. The reaction mixture was cooled and suspended in 5 ml of water, and conc. HCl was added dropwise with vigorous stirring to pH 5. After heating for 1 h at 0–5°C, the precipitate that formed was filtered off , washed with the smallest possible amount of ice water, and dried in a vacuum over P_2O_5. Compounds **Ia, Ic**–**Ii** were purified by crystallization from acetonitrile, and compound **Ib** was crystallized from acetone. Product **Ij** was extracted with 1,2-dichloroethane and finally crystallized from acetonitrile. Crystals of the compounds obtained were dried in a vacuum.

b. A mixture of 0.0022 mol of chloride **II** and 0.0022 mol of arylamine was heated at 120°C for 30 min. The solidified reaction mixture was crystallized from acetonitrile and dried in a vacuum.

6-Methyl-4-(4-methylphenyl)aminopyrimidin-2(1*H*)-one (IV). A mixture of 0.5 g of thioether **VII** and 0.34 g of 4-methylphenylamine was heated at 140°C until methanethiol no longer evolved. The reaction mixture was cooled, mechanically ground, crystallized from acetonitrile, and dried in a vacuum to obtain 0.32 g (46%) of compound **IV**, mp 241°C (decomp.), R_f 0.79. ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, Me), 2.27 s (3H, Me), 5.59 s (1H, CH), 7.06, 7.07 d (2H, Ar); 7.46, 7.47 d (2H, Ar), 8.55 br.s (1H, NH), 10.46 br.s (1H, NH). Found, %: C 65.73; H 6.05; N 19.69. $C_{12}H_{13}N_3O$. Calculated, %: C 66.96; H 6.09; N 19.52.

6-Methyl-4-(methylsulfanyl)pyrimidin-2(1*H*)-one (VII). To a solution of 2 g of thioxoketone **VI** in 18 ml of water containing 2 g of NaOH, methyl iodide, 2 g, was added with vigorous stirring. The reaction mixture was heated for 1 h at 40°C and then for 1 h at 70°C, after which it was cooled, filtered, and acidified with conc. HCl. The precipitate that formed was filtered off, washed with water, and dried under a stream of warm air for 5 h. Crystallization from acetonitrile and drying in a vacuum gave 1.05 g (48%) of compound **VII**, mp 229°C, R_f 0.82. ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, Me), 2.42 s (3H, SMe), 5.87 s (1H, CH), 12.36 s (1H, NH). Found, %: C 45.46; H 5.01; N 17.91. $C_6H_8N_2OS$. Calculated, %: C 46.14; H 5.16; N 17.93. Published data: mp 174–175°C [11] and 178–180°C [9]. According to our observations, the published melting points relate to only partial transfer of solid to liquid, while complete melting takes place only at our specified temperature.

2-(2-Acetoxyethyl)amino-6-methyl-4-cyclohexylaminopyrimidine (VIII). A mixture of 0.5 g of chloride **II** and 0.22 g of cyclohexylamine was heated for 1.5 h at 120°C. The reaction mixture was then crystallized from acetonitrile and allowed to stand –25°C for 1 h for complete precipitation. The precipitate that

formed was filtered off and dried in a vacuum to obtain 0.27 g (37%) of compound **VIII** hydrochloride, mp 122°C, R_f 0.84. ^{1}H NMR spectrum, δ, ppm: 1.12–2.91 m (17H, *cyclo*-C_6H_{11}, Ac, Me), 3.48 s (2H, CH_2), 4.09 t (2H, CH_2), 6.49 s (1H, CH), 7.53 s (1H, N^2H), 8.01 br.s (1H, N^4H). Found, %: C 52.44; H 6.86; N 17.00. $C_{15}H_{24}N_4O_2 \cdot HCl$. Calculated, %: C 54.74; H 7.60; N 17.03.

2-(2-Hydroxyethyl)amino-6-methyl-4-(4-methylphenyl)aminopyrimidine (IX). A mixture of 0.25 g of arylaminopyrimidine **Ic** and 10 ml of conc. HCl was heated at 60°C for 3 h and then evaporated to dryness. The dry residue was crystallized from propan-2-ol and dried in a vacuum over P_2O_5 to obtain 97 mg (44%) of compound **IX** hydrochloride, mp 217°C (decomp.). R_f 0.81. ^{1}H NMR spectrum, δ, ppm: 2.30 s (6H, Me, MeC_6H_4), 3.46 s (2H, CH_2), 3.56 and 3.57 d (2H, CH_2), 4.72 br.s (1H, OH), 6.19 s (1H, CH), 7.14 s (2H, Ar), 7.58 s (2H, Ar), 7.81 s (1H, N^2H), 10.72 br.s (2H, N^4H), 12.97 br.s (N^+H). Found, %: C 56.34; H 5.95; N 18.72. $C_{14}H_{18}N_4O \cdot HCl$. Calculated, %: C 57.04; H 6.50; N 19.01.

Arylaminopyrimidine **Ic**, 0.5 g, was added to a solution of 0.16 g of KOH in 5 ml of 50% aqueous ethanol. The reaction mixture was heated at 60°C for 3 h and then evaporated to dryness in a vacuum. The residue was diluted with 5 ml of acetone, and the precipitate that formed was filtered off. A solution of 0.33 g of picric acid in 5 ml of acetone was added to the filtrate. The resulting mixture was refluxed for 15 min and then cooled to 0°C. The precipitate was filtered off, crystallized from acetone, and dried in a vacuum to obtain 0.15 g (21%) of compound **IX** picrate, mp 202°C, R_f 0.85. ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, *Me*C_6H_4), 2.32 s (3H, Me), 3.44 d (2H, CH_2), 3.58 d (2H, CH_2), 4.80 br.s (1H, OH), 6.07 s (1H, CH), 7.15–8.54 m (7H, Ar, N^2H), 10.37 br.s (1H, N^4H), 11.87 br.s (1H, *H*OC_6H_2). Found, %: C 46.71; H 4.28; N 19.61. $C_{14}H_{18}N_4O \cdot C_6H_3N_3O_7$. Calculated, %: C 49.28; H 4.31; N 20.12.

2-(2-Acetoxyethyl)amino-6-methyl-4-(4-methylphenyl)aminopyrimidine (X). Arylaminopyrimidine **Ic**, 0.5 g, was added in portions with vigorous stirring to a solution of 0.25 g of NaOH in 10 ml of water. The resulting mixture was kept at room temperature for 3 h and then at 50°C for 1 h. A suspension formed and was cooled and filtered. The crystals were washed with water, crystallized from 40% aqueous ethanol, and dried in a vacuum over P_2O_5 to obtain 0.2 g (45%) of compound **X**, mp 145°C, R_f 0.68 (A). ^{1}H NMR spectrum, δ, ppm: 2.00 s (6H, Ar, *Me*C_6H_4), 2.26 s (3H, Me), 3.48 and 3.49 d (2H, CH_2), 4.11 and 4.13 d (2H, CH_2), 5.82 s (1H, CH), 6.52 br.s (1H, N^2H), 7.01 and 7.03 d (2H, Ar), 7.48 and 7.50 d (2H, Ar), 8.76 s (1H, N^4H). Found, %: C 63.68; H 6.65; N 18.41. $C_{10}H_{20}N_4O_2$. Calculated, %: C 63.98; H 6.71; N 18.65.

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