ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 4, pp. 818–824. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © A.V. Erkin, V.I. Krutikov, 2010, published in Zhurnal Obshchei Khimii, 2010, Vol. 80, No. 4, pp. 657–663.

Effect of Halogen Atom Localization on the Level of Antimycobacterial Activity of 2-Amino-4-arylamino-6-methylpyrimidines

A. V. Erkin and V. I. Krutikov

St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: kruerk@yandex.ru

Received November 11, 2009

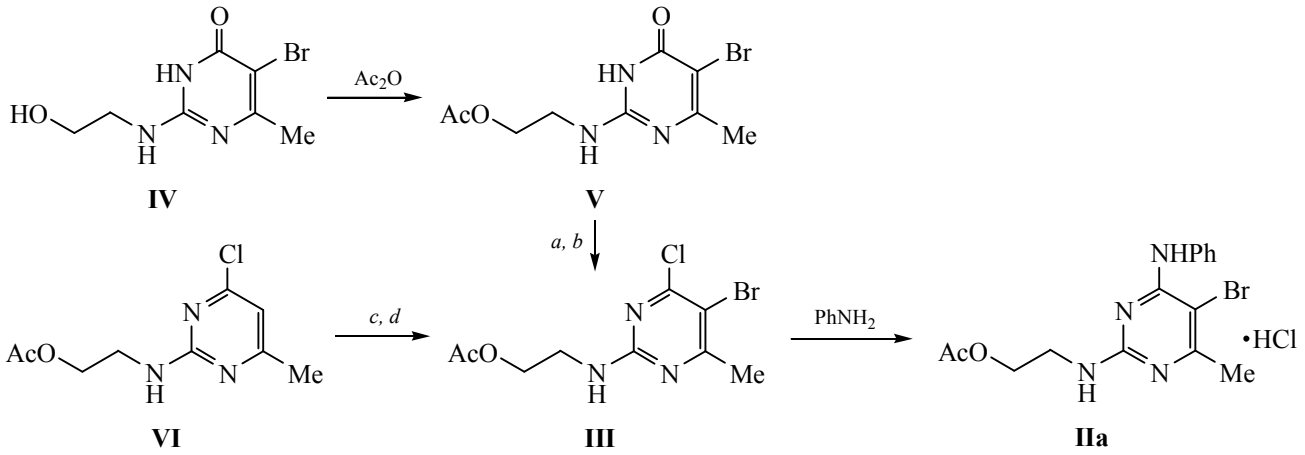
Abstract—Several hydrochlorides of 2-alkyl(cycloalkyl, aralkyl)-5-bromo-6-methyl-4-phenylaminopyrimidines have been synthesized as isosteric analogs of the corresponding 2-alkyl(cycloalkyl, aralkyl)-4-(3-bromophenyl)amino-6-methylpyrimidine hydrochlorides. Moving the bromine atom from the benzene ring into the heterocycle is accompanied by a significant decrease in the level of antimycobacterial activity.

DOI: 10.1134/S1070363210040237

Discovery of strong cell growth inhibitors of a *Mycobacterium smegmatis* strain among hydrochlorides of 2-(2-acetoxyethyl)amino-4-haloaryl-amino-6-methylpyrimidones [1] and their analogs [2] points to the obvious prospects of further search for new antibacterial agents among similar compounds.

In order to establish the impact of displacement of the halogen atom from the benzene ring of 2-amino-4-(3-bromophenyl)amino-6-methylpyrimidines hydrochlorides (**Ia–Ic**) into the heterocyclic frame on the level of their inhibitory action, we have synthesized hydrochlorides of 2-amino-5-bromo-6-methyl-4-phenylaminopyrimidines (**IIa–IIc**) and, having evaluated their antimycobacterial activity, compared these groups of compounds by the efficiency of the inhibition of the cell growth of the strain.

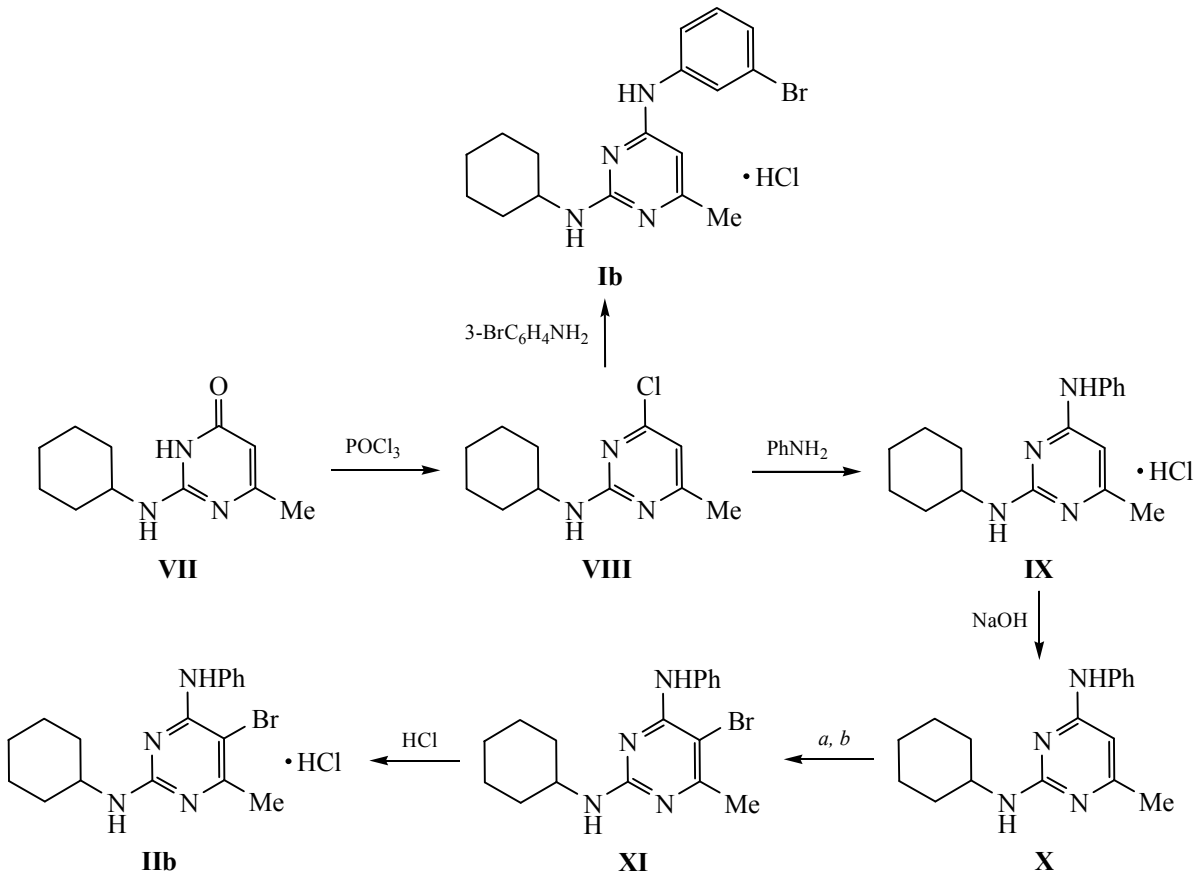
2-(2-Acetoxyethyl)amino-5-bromo-6-methyl-4-phenylaminopyrimidine hydrochloride (**IIa**) was obtained by amination of 2-(2-acetoxyethyl)amino-5-bromo-6-methyl-4-chloropyrimidine (**III**) with an equimolar amount of phenylamine without solvent at 100–110°C. The key product **III** was prepared starting from 5-bromo-2-(2-hydroxyethyl)amino-6-methylpyrimidin-4(3*H*)-one (**IV**), by acetylation in pyridine at 100°C followed by the exchange chlorination of 2-(2-acetoxyethyl)amino-5-bromo-6-methylpyrimidin-4(3*H*)-one (**V**), or alternatively by bromination of 2-(2-acetoxyethyl)amino-6-methyl-4-chloropyrimidine (**VI**) in accordance with the following scheme.

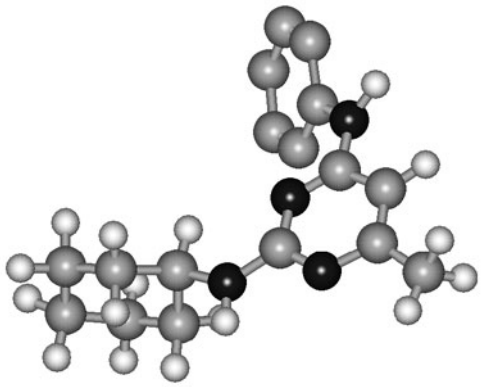


It should be noted that the exchange chlorination of bromopyrimidinone **V** allows the preparation of dihalopyrimidine **III** only in low yields, regardless of the type of chlorinating agent. On treating **V** with phosphorus oxychloride (method *a*), along with the target dihalopyrimidine **III** a significant amount of tars formed, and the yield after double crystallization was only 3–4%. The yield somewhat increases (up to 10%) when phosphorus pentachloride is used (method *b*), but this version of the reaction is also accompanied with a considerable tarring.

Higher yields of dihalopyrimidine **III** can be obtained by the direct bromination of aminochloropyrimidine **VI** with bromine in the presence of HBr acceptor, like triethylamine (method *c*), and especially by using *N*-bromosuccinimide (NBS) (method *d*) in carbon tetrachloride. Bonding the liberated hydrogen bromide and thereby shifting the reaction equilibrium toward formation of **III** is particularly important in view of reduced nucleophility of C^5 atom of the ring because of the influence of electron-withdrawing effect of a halogen atom.

We performed the synthesis of 5-bromo-6-methyl-4-phenylamino-2-cyclohexylaminopyrimidine hydrochloride (**IIb**), as well as previously unknown 4-(3-bromophenyl)amino-6-methyl-2-cyclohexylaminopyrimidine hydrochloride (**Ib**), using a multistage scheme, based on 6-methyl-2-cyclohexylaminopyrimidin-4(3*H*)-one hydrochloride (**VII**). Compound **VII** was subjected to exchange chlorination with phosphorus oxychloride to form 6-methyl-4-chloro-2-cyclohexylaminopyrimidine (**VIII**) followed by amination with equimolar amounts of phenyl- and 3-bromophenylamine in the absence of solvent at 100–110°C. The resulting 6-methyl-4-phenylamino-2-cyclohexylaminopyrimidine hydrochloride (**IX**) was reacted with an excess of aqueous sodium hydroxide to afford the free base **X**, which by treating with bromine (method *a*) or with *N*-bromosuccinimide (method *b*) in carbon tetrachloride was transformed into 5-bromo-6-methyl-4-phenylamino-2-cyclohexylaminopyrimidine (**XI**). Finally, hydrochloride **IIb** was prepared from the free base **XI** by the action of hydrochloric acid.





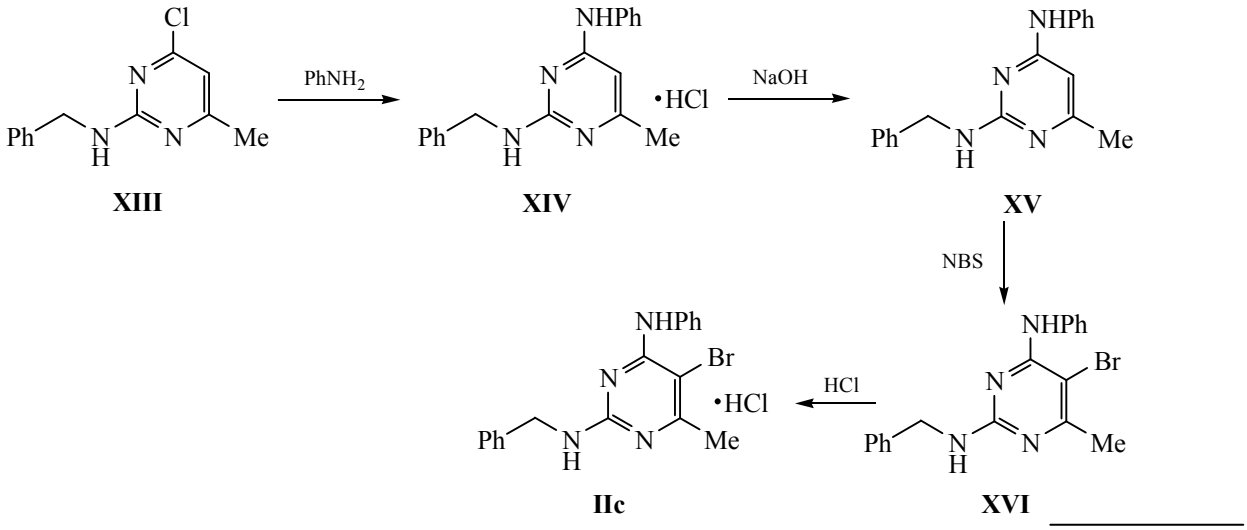
Quantum-chemical optimization of the geometry of the molecule of 6-methyl-4phenylamino-2-cyclohexylamino-pyrimidine (**X**).

Unlike the 2-benzylamine-6-methylpyrimidin-4(3*H*)-one [2] we could not isolate aminopyrimidinone **VII** in the form of a free base with acceptable yield by the interaction of 6-methyl-2-methylthiopyrimidin-4(3*H*)-one (**XII**) with cyclohexylamine. After removal of excess amine from the reaction mixture and crystallization of the residue from ethanol, we have obtained dequaternized compound **VII** in 23% yield. To isolate the remaining product we saturated the ethanol filtrate with dry hydrogen chloride and isolated aminopyrimidinone hydrochloride **VII** in 26% yield, calculated on the free base content.

The exchange chlorination of quaternized substrate **VII** was not accompanied by any difficulty, but because of the complexity of the vacuum distillation of small quantities of chloropyrimidine **VIII** we used this compound in the amination stage without purification.

The main disadvantage of bromination of the free base **X** is the low yield of the product **XI** obtained with the reaction both by way of *a,* and by the method *b.* This may be due primarily to the possibility of aromatic ring bromination [3] and to a lesser extent, to sterically hindrance to the attack of the bromine atom on the position 5 of the heterocycle. Indeed, the results of quantum-chemical geometry optimization of **X** indicated a significant distance between phenyl and pyrimidine nuclei and their noncoplanar location in space (see the figure).

For the preparation of 2-benzylamine-5-bromo-6-methyl-4-phenylamino-pyrimidine hydrochloride (**IIc**) we chose similar sequence of transformations to the above mentioned for 2-benzylamine-6-methyl-4-chloropyrimidine (**XIII**) presented in the scheme below.



The amination of compound **XIII** with equimolar amount of phenylamine in the absence of solvent at 100–110°C led to the hydrochloride of 2-benzylamino-6-methyl-4-phenylaminopyrimidine (**XIV**), the neutralization by an excess of aqueous sodium hydroxide gave free base **XV**. The latter by treating with *N*-bromosuccinimide was converted into 2-benzylamino-5-bromo-6-methyl-4-phenylaminopyrimidine (**XVI**) that was suspended in hydrochloric acid to give benzylaminobromopyrimidine hydrochloride **IIc**.

Since the bromination of the free base **X** with bromine has no obvious advantages over the use of *N*-bromosuccinimide and, moreover, can provide the

product **IIb** of reduced, according to its mp, purity, we have performed bromination of diaminopyrimidine **XV** exclusively with *N*-bromosuccinimide.

Structures of compounds **IIa–IIc** were confirmed by their ^{1}H NMR spectra containing signals of the protons of aliphatic and aromatic groups with characteristic chemical shifts. In the spectrum of acetoxyethylaminobromopyrimidine **IIa** there are unresolved signals of the protons of methylene groups at 3.45 and 4.0 ppm, and a multiplet of aromatic protons in the region of 7.2–7.5 ppm. The spectrum of **IIb** is characterized by the presence of multiplets of cyclohexane protons and phenyl rings in the regions of 0.9–1.9 and 7.2–7.5 ppm respectively. The spectrum of benzylaminobromopyrimidine **IIc** contains a multiplet in the region of 7.1–7.4 ppm with integral intensity corresponding to ten aromatic protons.

Moving the halogen atom from the aromatic ring of 2-(2-acetoxyethyl)amino-4-(3-bromophenyl)amino-6-methylpyrimidine hydrochloride **(Ia)** and bromophenylaminopyrimidine **Ib** into the heterocyclic nucleus causes a sharp decrease in antimycobacterial activity of 5-bromo-2,4-diaminopyrimidine hydrochlorides **IIa, IIb** (see the table). Benzylaminobromopyrimidine hydrochloride **IIc**, as well as hydrochloride of its isosteric analogue, 2-benzylamine-4-(3-bromophenyl) amino-6-methylpyrimidine (**Ic**) do not inhibit cell growth of the strain of *Mycobacterium smegmatis* in the concentration range of 0–100 mg ml^{-1}. The data obtained demonstrated the importance of maintaining the original configuration of **Ia, Ib** providing pharmacophore properties towards the given biological object.

The values of IC_{100}, providing 100% inhibition of cell growth of a *Mycobacterium smegmatis* strain

Comp. no.	IC_{100}, g l^{-1}	References
Ia	0.0125	[1]
Ib	0.010	–
Ic	> 0.100[a]	[2]
IIa	≥ 0.100	–
IIb	0.100	–
IIc	≥ 0.100	–

[a] The quantitative value of the concentration is given in addition to the cited paper's data.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer (operating frequency 400.13 MHz) in DMSO-d_6, with residual solvent protons as internal reference. TLC was carried out on Silufol UV-254 plates in the following systems: 1-butanol-acetic acid–water, 2:2:1 (A), 1-butanol-acetic acid–water, 1:1:1 (B), chloroform–methanol, 7:1 (C), chloroform–methanol, 9:1 (D), acetone-hexane, 2:1 (E), acetone–hexane plus 2 drops of pyridine (F), acetone–heptane, 1:1 (G), and 1-butanol-acetic acid–water, 2:1:1 (H). Elemental analysis was performed on a Hewlett-Packard B-185 CHN-analyzer. Water–ethanol solutions of hydrochlorides **Ib** and **IIa–IIc** gave a positive test when treated with aqueous silver nitrate.

Compound **IV** was synthesized by the method described in [4], compound **VI,** in accordance with [5], and compound **XIII,** according to [2]. Free bases **X** and **XV** were obtained by suspending the corresponding hydrochlorides **IX** and **XIV** in water containing a double molar excess of sodium hydroxide. The precipitated solid was filtered off, washed with water until the filtrate pH reached ~7, dried in a vacuum over phosphorus pentoxide to constant weight, and was used in the bromination stage without recrystallization.

Quantum-chemical optimization of the geometry of 6-methyl-4-phenylamino-2-cyclohexylaminopyrimidine (**X**) molecule was performed by Fletcher-Reeves method, using "HyperChem™ Release 6.03 for Windows Molecular Modeling System" software package.

4-(3-Bromophenyl)amino-6-methyl-2-cyclohexylaminopyrimidine (Ib). A mixture of 0.24 g of **VIII** and 0.19 g of 3-bromoaniline was heated at 100–110°C until solidification. The solid reaction product was mechanically crushed and crystallized from acetonitrile–ethanol (15:2) mixture. After drying in a vacuum over phosphorus pentoxide 71 mg (16%) of bromophenylaminopyrimidine **Ib** was obtained, mp 258°C (decomp.), R_f 0.72 (A). ^{1}H NMR spectrum, δ, ppm: 0.84–1.95 m (10H, *cyclo*-C_6H_{11}), 2.31 s (3H, Me), 3.81 s (1H, CH), 6.18 s (1H, CH_{pyr}), 7.27–8.25 m (4H, Ar), 7.47 s (1H, N^2H), 10.84 s (1H, N^4H). Found, %: C 50.94; H 5.43; N 13.89. $C_{17}H_{21}BrN_4 \cdot HCl$. Calculated, %: C 51.34; H 5.58; N 14.09. Isolated as hydrochloride.

2-(2-Acetoxyethyl)amino-5-bromo-6-methyl-4-phenylaminopyrimidine (IIa). A mixture of 0.17 g of **III** and 0.05 g of phenylamine was heated at 100–110°C until solidification. The solid reaction product was mechanically crushed and crystallized from

acetonitrile. After drying in a vacuum over phosphorus pentoxide 99 mg (45%) of acetoxyethylaminobromopyrimidine **IIa** was obtained, mp 164 0C, R_f 0.78 (B). ^{1}H NMR spectrum, δ, ppm: 1.97 s (3H, Me), 2.48 s (3H, Me), 3.45 s (2H, CH_2), 4.04 s (2H, CH_2), 7.20–7.51 m (5H, Ph), 7.98 s (1H, N^2H), 9.71 s (1H, N^4H). Found, %: C 44.15; H 4.21; N 13.67. $C_{15}H_{17}BrN_4O_2$·HCl. Calculated, %: C 44.85; H 4.52; N 13.95. Isolated as hydrochloride.

5-Bromo-6-methyl-4-phenylamino-2-cyclohexylaminopyrimidine (IIb). *a*. To a solution of 0.4 g of **X** in 5 ml of carbon tetrachloride 0.22 g of bromine in 2 ml of carbon tetrachloride was added dropwise with stirring. After the addition of bromine the reaction mixture was stirred at room temperature for 30 min and then evaporated in a vacuum to dryness. To the residue 5% aqueous sodium hydroxide solution was added, thoroughly mixed, the precipitate formed was filtered off, washed with water and was ground with 5 ml of concentrated hydrochloric acid to form a suspension. Water was partly removed in a vacuum to 3/4 of the initial volume, the precipitate was filtered off, dried at 60°C for 10 h, and crystallized from anhydrous 2-propanol to give after drying *in vacuo* over phosphorus pentoxide 46 mg (9%) of cyclohexylaminobromopyrimidine **IIb**, mp 214°C (decomp.), R_f 0.79 (A). ^{1}H NMR spectrum, δ, ppm: 0.88–1.87 m (10H, *cyclo*-C_6H_{11}), 2.45 s (3H, Me), 3.51 s (1H, CH), 7.19–7.53 m (5H, Ph), 7.99 s (1H, N^2H), 9.68 s (1H, N^4H). Found, %: C 50.55; H 5.23; N 13.71. $C_{17}H_{21}BrN_4$·HCl. Calculated, %: C 51.34; H 5.58; N 14.09. Isolated as hydrochloride.

Method *b*. A mixture of 0.5 g of **X** and 0.32 g of *N*-bromosuccinimide in 10 ml of carbon tetrachloride was boiled for 1 h, then evaporated in a vacuum to dryness. The residue was ground with 5 ml of diluted (1:1) hydrochloric acid, the suspension formed was concentrated *in vacuo* to 1/4 of the initial volume, filtered, and crystallized from ethanol. After drying in a vacuum over phosphorus pentoxide 84 mg (12%) of **IIb** were obtained, mp 217°C (decomp.), mp of the mixed sample, obtained by methods *a* and *b*: 216°C.

2-Benzylamine-5-bromo-6-methyl-4-phenylaminopyrimidine (IIc). A mixture of 0.83 g of **XV** and 0.51 g of *N*-bromosuccinimide in 20 ml of carbon tetrachloride was boiled for 1 h, then evaporated in a vacuum to dryness. The crystalline residue was ground with 10 ml of diluted (1:1) hydrochloric acid, filtered off, washed with a small amount of cold water, and crystallized twice from ethanol. After drying *in vacuo* over phosphorus pentoxide 0.34 g (29%) of benzylaminobromopyrimidine **IIc** was obtained, mp 202°C, R_f 0.80 (B). ^{1}H NMR spectrum, δ, ppm: 2.49 s (3H, Me), 4.39 s (2H, CH_2), 7.11–7.38 m (10H, Ph), 8.56 s (1H, N^2H), 9.69 s (1H, N^4H). Found, %: C 52.81; H 4.34; N 13.65. $C_{18}H_{17}BrN_4$·HCl. Calculated, %: C 53.29; H 4.47; N 13.81. Isolated as hydrochloride.

2-(2-Acetoxyethyl)amino-5-bromo-6-methyl-4-chloropyrimidine (III). *a.* A mixture of 0.7 g of **V** and 5 ml of freshly distilled phosphorus oxychloride was boiled for 3 h. After distilling off the excess of phosphorus oxychloride in a vacuum to the residue finely crushed ice was added and to thus formed suspension 25% aqueous ammonia solution was added until stable weakly basic reaction. The precipitate formed was filtered off and crystallized from ethanol. The purified product was dissolved in 10 ml of diethyl ether, insoluble substance was filtered off, and the filtrate was concentrated *in vacuo* to 1/2 of its initial volume and cooled to –25°C. The precipitate formed was filtered off and washed with a minimal amount of diethyl ether cooled to the same temperature. After drying in a vacuum 26 mg (3.4%) of dihalopyrimidine **III** was obtained, mp 144 0C, R_f 0.67 (B). ^{1}H NMR spectrum, δ, ppm: 2.00 s (3H, Ac), 2.45 s (3H, Me), 3.47, 3.50 (2H, CH_2), 4.09 m (2H, CH_2), 7.69 br.s (1H, NH). Found, %: C 34.88; H 3.47; N 13.46. $C_9H_{11}BrClN_3O_2$. Calculated, %: C 35.03; H 3.59; N 13.62.

b. A mixture of 1.6 g of **V** and 1.2 g of phosphorus pentachloride was heated at 130°C to homogenisation. To the cooled reaction mixture finely crushed ice was added, the mixture was treated with 25% aqueous ammonia solution till stable basic pH, and was ground to form precipitate that was filtered off, washed with cold water, and dried *in vacuo* over phosphorus pentoxide. The dry product was dissolved in 20 ml of boiling benzene, treated with activated alumina, and filtered. The filtrate was evaporated in a vacuum to dryness, and the resulting crystalline residue was recrystallized from 80% aqueous ethanol. After drying in a vacuum 0.25 mg (15%) of dihalopyrimidine **III** was obtained, mp 141°C, R_f 0.67 (B). Mp of the mixed sample of the product obtained by methods of *a* and *b*: 144°C.

c. To a solution of 0.5 g of **VI** in 10 ml of carbon tetrachloride heated to 60°C 0.12 g of bromine in 5 ml of carbon tetrachloride was added dropwise under stirring. The mixture was kept at the same temperature for further 30 min, then decanted from the precipitated

tars, and cooled. The precipitate was filtered off and crystallized from 80% aqueous ethanol. After drying in vacuum 0.19 mg (27%) of dihalopyrimidine **III** was obtained, mp 143°C, R_f 0.67 (B).

d. A mixture of 0.5 g of **VI** and 0.39 g of *N*-bromosuccinimide in 15 ml of carbon tetrachloride was boiled for 1 h. On cooling to room temperature the suspension formed was kept at 5°C for 1 h, filtered off, and crystallized from 80% aqueous ethanol. After drying in a vacuum 0.29 mg (43%) of dihalopyrimidine **III** were obtained, mp 145°C, R_f 0.67 (B). Mp of the mixed sample of the product obtained by methods of *c* and *d*: 144 0C.

2-(2-Acetoxyethyl)amino-5-bromo-6-methylpyrimidine-4(3*H*)-one (V). To a suspension of 2.9 g of **IV** in 10 ml of anhydrous pyridine heated to 85°C 1.84 g of acetic anhydride was added dropwise with vigorous stirring. The reaction mixture was kept at 100°C for 1 h, cooled, the precipitate was filtered off, washed with water, and crystallized from water. After drying *in vacuo* over phosphorus pentoxide 1.79 g (52%) of bromopyrimidinone **V** were obtained, mp 184°C, R_f 0.43 (D). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, Ac), 2.24 s (3H, Me), 3.47, 3.49, 3.52, 3.55 (2H CH_2), 4.07, 4.09, 4.12 (2H, CH_2), 6.49 br.s (1H, N*H*CH_2CH_2), 11.09 s (1H, NH). Found, %: C 33.78; H 3.92; N 14.27. $C_9H_{12}BrN_3O_3$. Calculated, %: C 37.26; H 4.17; N 14.48.

6-Methyl-2-cyclohexylaminopyrimidin-4(3*H*)-one (VII). A mixture of 3.12 g of **XII** and 5.94 g of cyclohexylamine was heated at 160°C for 5 h in an autoclave. On cooling the mixture was diluted with 10 ml of anhydrous ethanol, and strong air stream was passed through to remove methanethiol. After evaporation *in vacuo* to dryness the residue was diluted with 10 ml of anhydrous ethanol, brought to boiling and cooled to room temperature and then stored at –25°C for 1 h. The precipitate formed was filtered off and recrystallized from ethanol. After drying *in vacuo* over phosphorus pentoxide 0.97 g (23%) of aminopyrimidinone **VII** was obtained, mp 110°C ([6]: mp 230–232°C), R_f 0.32 (D). ^{1}H NMR spectrum, δ, ppm: 1.20–1.87 m (10H, *cyclo*-C_6H_{11}), 2.00 s (3H, Me), 3.69 s (1H, CH), 5.37 s (1H, CH_{pyr}), 6.34 br.s (1H, NH), 10.25 br.s (1H, NH_{pyr}). Found, %: C 63.47; H 8.02; N 20.17. $C_{11}H_{17}N_3O$. Calculated, %: C 63.74; H 8.27; N 20.27.

The ethanol filtrate after separation of compound **VII** was saturated with dry hydrogen chloride to form suspension that was concentrated *in vacuo* to 1/2 of the initial volume, cooled to –25°C, the precipitate was filtered off and recrystallized from anhydrous ethanol. After drying in a vacuum over phosphorus pentoxide 1.27 g (26%) of aminopyrimidinone hydrochloride **VII** was obtained, mp 200°C ([7]: mp 200ºC), R_f 0.25 (E).

6-Methyl-4-chloro-2-cyclohexylaminopyrimidine (VIII). A mixture of 1.6 g of hydrochloride salt of **VII** and 20 ml of freshly distilled phosphorus oxychloride was boiled for 1 h. After that, the excess of phosphorus oxychloride was distilled off in a vacuum, the residue was treated with finely crushed ice, the precipitated oily suspension was alkalinized with 25% aqueous ammonia solution and extracted with dichloromethane (2×20 ml). The extract was dried over anhydrous sodium sulfate overnight, filtered, and evaporated to dryness at atmospheric pressure to give 1.3 g (87%) of chromatographically pure [R_f 0.54 (F)] chloropyrimidine **VIII** that was used in the next stage without additional purification.

6-Methyl-4-phenylamino-2-cyclohexylaminopyrimidine (IX). A mixture of 1.3 g of **VIII** and 0.54 g of phenylamine was heated at 100–110°C until solidification. The residue was mechanically ground and crystallized from acetonitrile. After drying in a vacuum 0.65 g (35%) of phenylaminopyrimidine **IX** was obtained, mp 229°C (decomp.), R_f 0.73 (A). ^{1}H NMR spectrum, δ, ppm: 0.84–1.98 m (10H, *cyclo*-C_6H_{11}), 2.29 s (3H, Me), 3.78 s (1H, CH), 6.18 s (1H, CH_{pyr}), 7.12–7.70 m (5H, Ar), 8.31 s (1H, N^2H), 10.70 c (1H, N^4H). Found, %: C 63.51; H 6.92; N 17.33. $C_{17}H_{22}N_4$·HCl. Calculated, %: C 64.04; H 7.27; N 17.57. Isolated as hydrochloride.

2-Benzylamino-6-methyl-4-phenylaminopyrimidine (XIV). A mixture of 1 g of **XIII** and 0.4 g of phenylamine was kept at 100–110°C until solidification. The solid residue was mechanically ground and crystallized from ethanol. After drying in a vacuum 0.96 g (68%) of phenylaminopyrimidine **XIV** was obtained, mp 242°C (decomp.), R_f 0.69 (H). ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, Me), 4.60 s (2H, CH_2), 6.23 s (1H, CH), 7.03–7.50 m (10H, Ph), 8.56 s (1H, N^2H), 10.77 s (1H, N^4H). Found, %: C 65.91; H 5.69; N 17.02. $C_{18}H_{18}N_4$·HCl. Calculated, %: C 66.15; H 5.86; N 17.14. Isolated as hydrochloride.

ACKNOWLEDGMENTS

The authors express their deep gratitude to Prof. V.V. Tets with coworkers (Pavlov St. Petersburg State Medical University) for microbiological assays, and to O.V. Kozlova for participation in the work.

REFERENCES

1. Erkin, A.V. and Krutikov, V.I., *Zh. Obshch. Khim.,* 2007, vol. 77, no. 11, p. 1887.
2. Erkin, A.V., Krutikov, V.I., and Smirnova, E.B., *Zh. Obshch. Khim.,* 2008, vol. 78, no. 10, p. 1708.
3. Nishiwaki, T., *Chem. Pharm. Bull*., 1962, vol. 10, no. 11, p. 1029.
4. Erkin, A.V., Krutikov, V.I., and Kosykh, A.V., *Zh. Obshch. Khim.,* 2005, vol. 75, no. 11, p. 1898.
5. Erkin, A.V., and Krutikov, V.I., *Zh. Obshch. Khim.,* 2006, vol. 76, no. 3, p. 501.
6. Botta, M., De Angelis, F., Finizia, G., Gambacorta, A., and Nicoletti, R., *Synth. Commun*., 1985, vol. 15, no. 1, p. 7.
7. Erkin, A.V., Krutikov, V.I., and Pavlovich, N.I., *Zh. Obshch. Khim.,* 2003, vol. 73, no. 3, p. 494.