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Synthesis and Biological Activity of Hydrochlorides of Benzyl Ethers of Pyrimidin-4(3*H*)-thiones and Related Compounds

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Abstract—Hydrochlorides of benzyl ether of 2-amino-6-methylpyrimidin-4(3*H*)-thione and its analogs were synthesized and biological activity of the synthesized compounds was studied.

Keywords: pyrimidin-4(3*H*)-thione, benzylation, hydrochloride, antifungal activity

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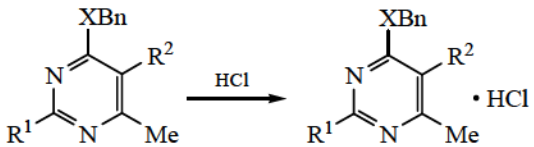
Among effective inhibitors of biological objects of viral and microbial nature pyrimidin-4(3*H*)-thiones and their ethers with various substituents in the ring attract great attention [1–3]. Some representatives of these compounds were considered earlier [4, 5] as potential antitumor agents. In continuation of the studies of the pyrimidin-4(3*H*)-thione derivatives, in the present work we have synthesized hydrochlorides of 2-amino-4-benzylthio-6-methylpyrimidine (**Ia**) and its analogs (**Ib**–**Ie**), and their biological activity towards a series of pathogenic cultures, *Escherichia coli*, *Mycobacterium tuberculosis*, and *Candida albicans*, was studied (Scheme 1).

Hydrochlorides **Ia**–**Id** were obtained by passing gaseous hydrogen chloride through the solutions of the corresponding free bases **IIa**–**IId** in anhydrous benzene at room temperature. Compound **Id** could not be isolated in crystalline state because of its high hygroscopicity. The treatment of the oily substance of this hydrochloride with excess of 25% aqueous ammonia led to regeneration of the starting benzyloxypyrimidine **IId**.

The formation of 2-amino-4-benzylamino-6-methylpyrimidine hydrochloride **Id** occurred directly at the condensation of 2-amino-4-chloro-6-methylpyrimidine (**III**) with benzylamine in 1 : 1 molar ratio of the components in the absence of solvent at 130°C (Scheme 2).

Limiting the time of contact of 2-amino-6-methylpyrimidin-4(3*H*)-one (**IV**) with phosphorus oxy-

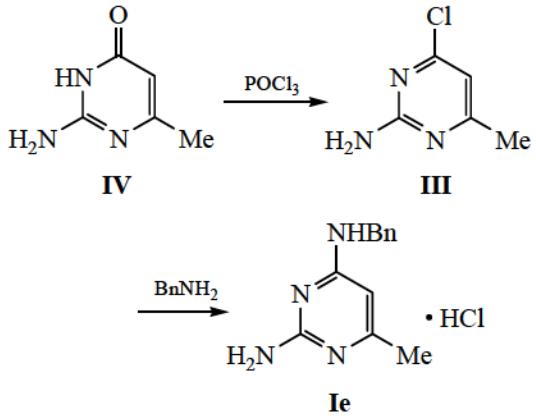
Scheme 1.



IIa–IId **Ia–Id**

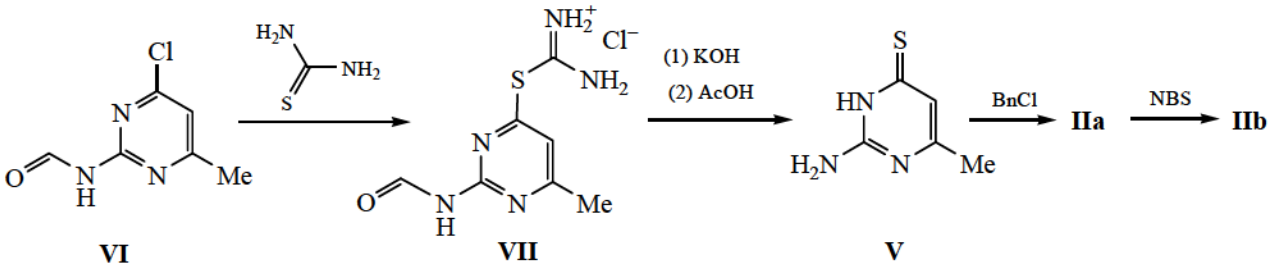
$R^1 = H_2N$, $R^2 = H$, X = S (**a**); $R^1 = H_2N$, $R^2 = Br$, X = S (**b**); $R^1 = R^2 = H$, X = S (**c**); $R^1 = H_2N$, $R^2 = H$, X = O (**d**); Bn = $PhCH_2$.

Scheme 2.

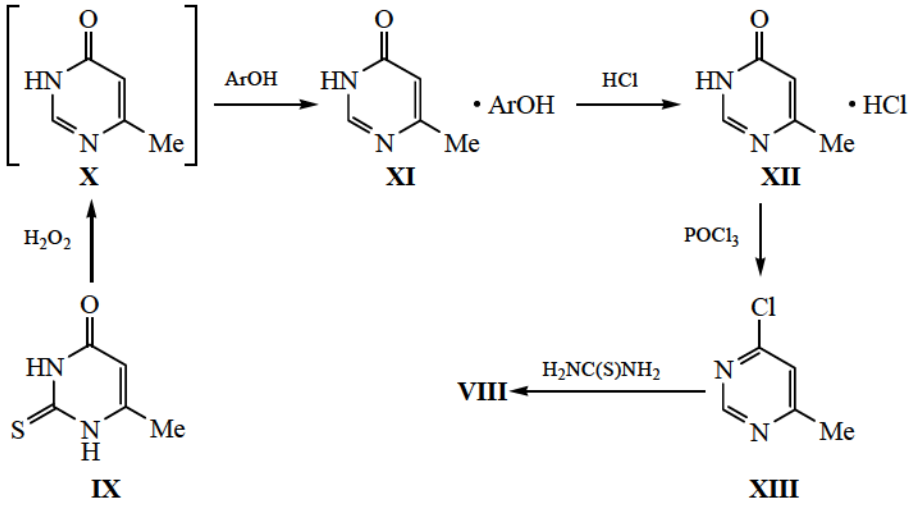


IV **III** **Ie**

Scheme 3.



Scheme 4.



Ar = 2,4,6-$(O_2N)_3C_6H_2$.

chloride to the period of homogenization of the reaction mixture allowed to avoid the processes of N- and O-phosphorylation, which were noted in [6] during the exchange chlorination of compound (**IV**) by the method described in [7].

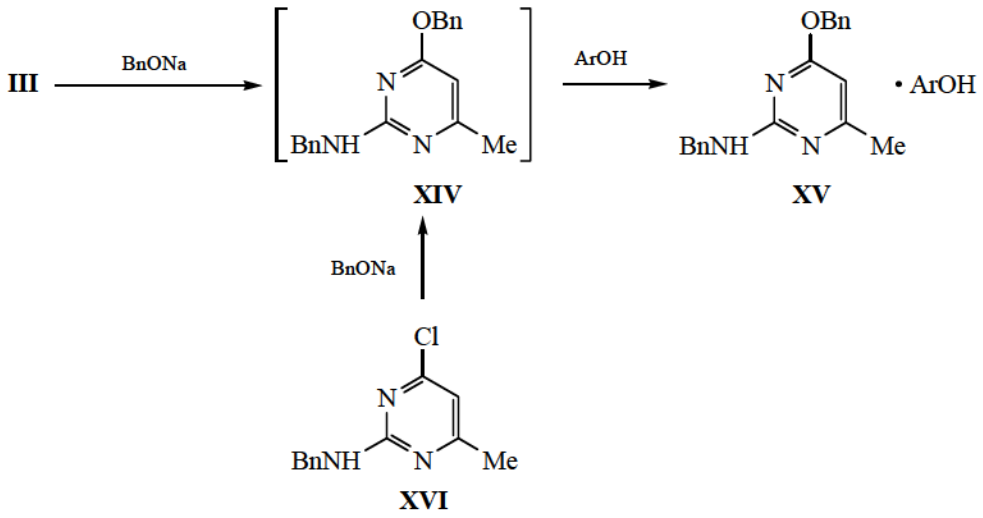
The synthesis of free bases **IIa, IIb** was performed by S-benzylation of 2-amino-6-methylpyrimidin-4(3*H*)-thione (**V**) with benzyl chloride in aqueous ethanol solution in the presence of sodium hydroxide with subsequent bromination of compound **IIa** with *N*-bromosuccinimide (NBS) in tetrachloromethane (Scheme 3).

Isothiocytosine **V** required for the reaction was prepared by alkaline hydrolysis of isothiouronium salt **VII**, which was obtained by condensation of 4-chloro-2-formylamino-6-methylpyrimidine (**VI**) [6] with thiourea in boiling ethanol. The IR spectrum of compound **VII** contained the bands of stretching vibrations of the quaternized amidinium fragment in the range 2603–2652 and 2340–2360 cm^{-1}, as well as the bands "amide **I**" and "amide **II**" at 1664 and 1549 cm^{-1} respectively.

The use of pyrimidine **VI** in the reaction allows to avoid the formation of bis(2-amino-6-methylpyrimidin-4-yl)sulfide at heating compound **III** with thiourea in ethanol [8]. Other methods of synthesis of isothiocytosine **V** included treatment of aminochloropyrimidine **III** with sodium hydrosulfide in ethylene glycol [5] and sulfidation of compound **IV** with the Lawesson reagent, 2,4-bis(4-methoxyphenyl)-[1,2,3,4]-dithiadiphosphetane-2,4-disulfide, in 1,4-dioxane [9]. Taking into account the necessity of preliminary preparation of the above sulfidating reagents [5, 9], and of performing the reaction in a heterogeneous medium [9], the aforementioned methods seem hardly acceptable.

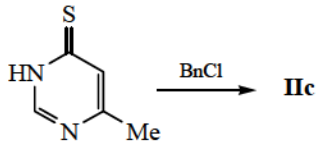
The synthesis of free base **IIc** included S-benzylation of 6-methylpyrimidin-4(3*H*)-thione (**VIII**) under the conditions described for isothiocytosine **V**. Thiopyrimidine **VIII**, in turn, was prepared by

Scheme 5.



Ar = 2,4,6-$(O_2N)_3C_6H_2$.

successive transformations of compounds **IX**–**XIII** according to method [10] modifying some stages.



Oxidative desulfurization of 6-methyl-2-thioxo-1,2-dihydropyrimidin-4(3*H*)-one (**IX**) with hydrogen peroxide in water gave 6-methylpyrimidin-4(3*H*)-one (**X**) isolated from the reaction mixture as picrate **XI**. The hydrolysis of complex compound **XI** with conc. hydrochloric acid resulted in the formation of hydrochloride of 6-methylpyrimidin-4(3*H*)-one **XII**, which after treatment with phosphorus oxychloride was converted into 4-chloro-6-methyl **XIII**. The condensation of chloropyrimidine **XIII** with thiourea in ethanol led directly to thiopyrimidine **VIII**; no formation of the intermediate isothiouronium salt was observed [10] (Scheme 4).

We have modified the stages of isolation and exchange chlorination of pyrimidinone **X**. In view of a high volatility [11], compound **X** was isolated from aqueous solution as picrate **XI**. By the same reason, the exchange chlorination was performed with hydrochloride **XII** rather than pyrimidinone **X**.

The free base **IId** was obtained by heating the mixture of aminochloropyrimidine **III** with 3-fold excess of sodium benzylate in benzyl alcohol at 140°C. The reaction proceeded as *N*-benzylation of the substrate with the formation of 2-benzylamino-4-benzyloxy-6-methylpyrimidine **XIV**, which was isolated in the crystalline form after the treatment of the reaction mixture with picric acid (method *a*). ^{1}H NMR spectrum of picrate **XV** contains characteristic signals of protons of CH_2 and NH groups in the region 4.6–5.5 ppm and at 8.6 ppm, respectively, with the integral intensity ratio 4 : 1. Finally, compound **XV** was identified by coincidence of its physicochemical and spectral parameters with those determined for the authentic sample of picrate **XV**. The latter was prepared by authentic synthesis, that is, by the reaction of 2-benzylamino-4-chloro-6-methylpyrimidine (**XVI**) [12] with 3-fold excess of sodium benzylate in benzyl alcohol at 140°C with a subsequent quaternization of *N,O*-dibenzylisocytosine **XIV** with picric acid (method *b*). Examples of successful *N*-benzylation of some (hetero)aromatic amines with benzyl alcohol under similar conditions are described in the literature [13] (Scheme 5).

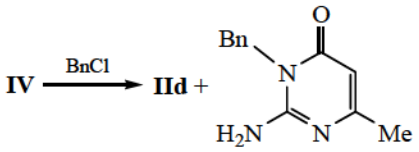
An attempt to displace the chlorine atom in the formyl derivative of aminochloropyrimidine **III** by the benzyloxy group failed. After completion of heating the reaction mixture of compound **VI** with 3-fold excess of sodium benzylate in benzyl alcohol at 140°C during 4 h a product was isolated, which was chromatographically identical to the initial substrate; the mixing probe with compound **VI** showed no depression of the melting point. The same result was obtained when DMF was used as the solvent.

Crystallography data and structure refinement parameters for 2-amino-3-benzyl-6-methylpyrimidin-4(3*H*)-one (**XVII**)

Parameter	Value
Formula	$(C_{12}H_{13}N_3O)_2 \cdot H_2O$
Crystal system	Monoclinic
a, Å	14.7885(6)
b, Å	9.9806(3)
c, Å	17.3608(7)
α, deg	90
β, deg	114.864(5)
γ, deg	90
V, Å^3	2324.88(17)
Molecular mass	448.52
Space group	$P2_1/c$
μ, mm^{-1}	0.088
Temperature, K	100(2)
Z	4
d_{calc}, g/cm^3	1.281
Crystal size, mm^3	0.25×0.18×0.14
Radiation	MoK_α
Total reflections	21307
Independent reflections	5327
Range of measurements 2θ, deg	5.09–55.00
Reflections with $\|F_0\| \geq 4\sigma_F$	3929
R_{int}	0.0516
R_σ	0.0675
R_1 ($\|F_0\| \geq 4\sigma_F$)	0.0480
wR_2 ($\|F_0\| \geq 4\sigma_F$)	0.0951
R_1 (for all data)[a]	0.0740
wR_2 (for all data)[b]	0.1080
S	1.056
ρ_{min}, ρ_{max}, e/Å^3	–0.261, 0.247

[a] $R_1 = \Sigma||F_0| - |F_c||/\Sigma|F_0|$. [b] $wR_2 = \{\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]\}^{1/2}$; $w = 1/[\sigma^2(F_0^2) + (aP)^2 + bP]$, where $P = (F_0^2 + 2F_c^2)/3$; $s = \{\Sigma[w(F_0^2 - F_c^2)]/(n - p)\}^{1/2}$, where n denotes the number of reflections and p is the number of refined parameters.

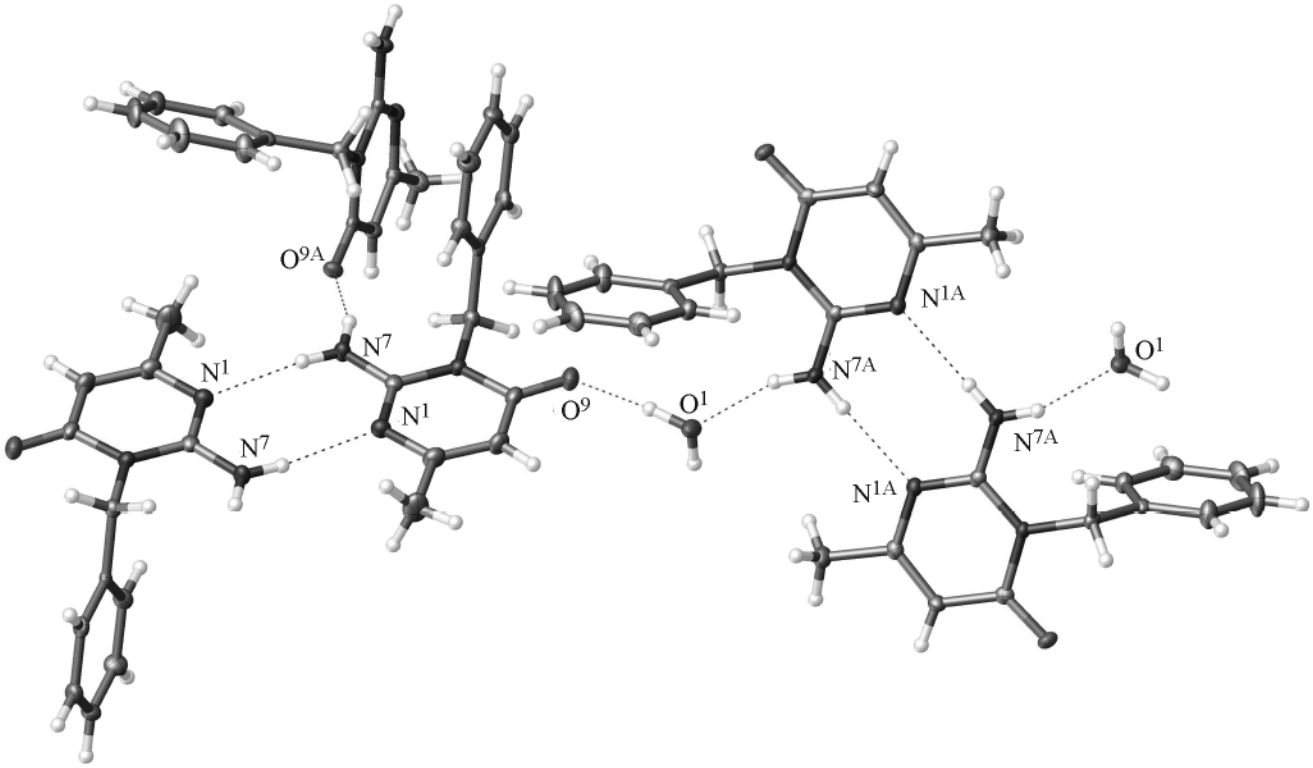
An alternative method for the preparation of the free base **IId** consisted in *O*-benzylation of isocytosine **IV** with benzyl chloride in DMF in the presence of sodium hydride [14, 15]. The replacement of the latter by the more available potassium carbonate resulted in the formation of the mixture of compound **IId** and 2-amino-3-benzyl-6-methylpyrimidin-4(3*H*)-one (**XVII**) as a minor product, which was separated by fractional crystallization.



XVII

The structure of *N*-benzylisocytosine **XVII** was proved by X-ray diffraction (XRD) analysis. According to the XRD (see the table), the crystal of compound **XVII** consists of the dimers of crystallographically equivalent molecules connected by hydrogen bonds between the proton of the exocyclic atom N^7 and atom N^1 of the adjacent molecule. The formation of the crystal lattice of *N*-benzylisocytosine **XVII** occurs by binding the dimers through H-bonding interactions between the oxygen atom O^9 of one monomer unit, the proton of crystallization water, the oxygen atom of the latter, and the proton of N^{7A} atom of another unit (see the figure). The formation of hydrogen bonds of the above-mentioned type can explain the splitting of the C=O group stretching vibration bands and bending vibrations of the amino group observed in the IR spectrum of the crystalline sample of compound **XVII**.

The results of biological screening of hydrochlorides **Ia**–**Ic, Ie** showed their inability to inhibit the cell growth of *Escherichia coli* and *Mycobacterium tuberculosis* in concentrations up to 100 mkg/mL. At the same time, compound **Ia** showed a pronounced antifungal activity with respect to *Candida albicans* [minimal concentration leading to 100% inhibition of the biological object (MIC_{100}) was 25 μg/mL]. Compound **Ib** was inactive in the range of concentrations 1–100 μg/mL. In going from hydrochloride **Ia** to compound **Ic** the value of MIC_{100} increased twice. Formal replacement of the sulfur atom in hydrochloride **Ia** by the secondary amino group was followed by the loss of antifungal activity of compound **Ie** in the above range of concentrations.



Structure of crystal lattice of 2-amino-3-benzyl-6-methylpyrimidin-4(3*H*)-one (**XVII**).

EXPERIMENTAL

^{1}H NMR spectra were registered on a Bruker WM-400 spectrometer (working frequency 400.13 MHz) in DMSO-d_6, the signals of residual protons of the solvent served as internal reference. IR spectra were taken on a Shimadzu FTIR-8400S spectrophotometer in KBr. The purity and identity of the compounds were monitored by TLC on Silufol UV-254 and Sorbfil PTSKh-AF-V-UV plates (compounds **IId**, **III**, and **XVII**) in the systems 1-butanol–acetic acid–water, 1 : 1 : 1 (eluent A), 2-propanol–25% aqueous ammonia, 3 : 1 (eluent B), acetone–hexane, 1 : 1 (eluent C), and acetone–hexane, 2 : 1 (eluent D). The plates were visualized by UV irradiation at 254 nm. Elemental analyses were performed on a Hewlett Packard 185B CHN-analyzer. Aqueous or aqueous-ethanol solutions of hydrochlorides **Ia**–**Ie** and **XII**, as well as of salt **VII** gave positive test on the presence of chloride ions when treated with aqueous silver nitrate.

X-ray structural analysis was performed in the Resource center of St. Petersburg State University "X-ray diffraction Studies" using the Agilent Technologies Excalibur Eos single crystal diffractometer equipped with CCD-detector. The measurements were performed at 100 K using monochromated MoK_α-radiation. The elementary cell parameters (see the table) were refined by the least-squares method from 21307 reflections with 2θ varied from 5.09° to 55.00°. The structure was solved by the direct method and refined to R_1 0.048 (wR_2 0.095) for 3929 independent reflections with $|F_0| \geq 4\sigma_F$ using SHELXL-97 program [16] implemented in OLEX2 package [17]. Extinction corrections were performed using program package CrysAlisPro [18]. The positions of hydrogen atoms were calculated using SHELX software, where U_{iso}(H) = 1.5U_{eq}(C) and C–H 0.96 Å for CH_3 groups, U_{iso}(H) = 1.2U_{eq}(C) and C–H 0.97 Å for CH_2 groups, U_{iso}(H) = 1.2U_{eq}(C) and C–H 0.93 Å for CH groups and U_{iso}(H) = 1.2U_{eq}(N) and N–H 0.86 Å for NH_2 groups. Hydrogen atoms of crystallization water molecule were localized objectively and refined without restrictions with individual thermal parameters. Crystallographic data and structure refinement parameters were deposited to the Cambridge Crystallographic Data Centre (CCDC 1018711) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

2-Amino-4-benzylthio-6-methylpyrimidine hydrochloride (Ia). Through a solution of 0.15 g of 2-amino-4-benzylthio-6-methylpyrimidine **IIa** in 15 mL of anhyd-

rous benzene dry hydrogen chloride was passed to saturation. After removal of the solvent in a vacuum the residue was treated with 5 mL of cyclohexane, the precipitate was filtered off and dried to a constant mass. Yield 0.12 g (70%), mp 180°C, R_f 0.76 (A). Found, %: C 53.15; H 5.21; N 15.59. $C_{12}H_{13}N_3S{\cdot}HCl$. Calcd, %: C 53.82; H 5.27; N 15.69.

2-Amino-4-benzylthio-5-bromo-6-methylpyrimidine hydrochloride (Ib). Through a solution of 0.13 g of 2-amino-4-benzylthio-5-bromo-6-methylpyrimidine **IIb** in 15 mL of anhydrous benzene dry hydrogen chloride was passed to saturation. The formed suspension was filtered, the filtrate was concentrated in a vacuum to half of the initial volume, the formed precipitate was filtered off, combined with the main portion of the product, washed with 5 mL of cyclohexane, and dried to a constant mass. Yield 80 mg (57%), mp 184°C, R_f 0.88 (A). Found, %: C 41.29; H 4.05; N 11.82. $C_{12}H_{12}BrN_3S{\cdot}HCl$. Calculated, %: C 41.58; H 3.78; N 12.12.

4-Benzylthio-6-methylpyrimidine hydrochloride (Ic). To a solution of 0.3 g of thiopyrimidine **VIII** in 18 mL of water containing 2 g of sodium hydroxide 0.3 g of benzyl chloride in 3 mL of ethanol was added dropwise with vigorous stirring. The mixture was kept at 80°C for 1 h and cooled to room temperature. 4-Benzylthio-6-methylpyrimidine **IIc** formed as an oily substance was extracted with 20 mL of benzene. The organic layer was separated and dried over calcium chloride for 1 day. The drier was separated, dry hydrogen chloride was passed through the solution to saturation, benzene was removed in a vacuum, the residue was treated with 10 mL of the 1 : 1 mixture of benzene and cyclohexane. The precipitate was washed with 5 mL of cyclohexane and dried to a constant mass. Yield 0.35 g (59%), mp 147°C, R_f 0.85 (A). ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, Me), 4.52 s (2H, CH_2), 7.24–7.44 m (5H, Ph), 7.58 s (1H, C^5H), 9.00 s (1H, C^2H). Found, %: C 56.59; H 4.87; N 10.77. $C_{12}H_{12}N_2S{\cdot}HCl$. Calculated, %: C 57.02; H 5.18; N 11.08.

2-Amino-4-benzylamino-6-methylpyrimidine hydrochloride (Ie). The mixture of 0.5 g of aminochloropyrimidine **III** and 0.37 g of freshly distilled benzylamine was kept at 130°C for 1 h. After cooling, the solidified reaction mass was crushed, dispersed in benzene, and filtered. The precipitate was crystallized from the mixture benzene–ethanol (7 : 1) and dried to a constant mass. Yield 0.5 g (57%), mp 156°C, R_f 0.80 (A). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 4.59 d (2H, CH_2NH, J 6.0 Hz), 6.00 s (1H, CH), 7.23–7.66 m (7H, Ph, NH_2), 9.21 t (1H, NH, J 11.0 Hz), 12.75 br.s (1H, N^+H). Found, %: C 57.13; H 6.18; N 22.14. $C_{12}H_{14}N_4{\cdot}HCl$. Calculated, %: C 57.48; H 6.03; N 22.35.

2-Amino-4-benzylthio-6-methylpyrimidine (IIa). To a solution of 0.4 g of isothiocytosine **V** in 10% aqueous sodium hydroxide prepared from 2 g of NaOH 0.34 g of benzyl chloride in 3 mL of ethanol was added dropwise at vigorous stirring. The mixture was kept at 80°C for 1 h, cooled, and the formed slurry was filtered. The precipitate was washed with water, dried at 70°C for 4 h, crystallized from cyclohexane, and dried to a constant mass. Yield 0.41 g (62%), mp 123°C (mp 118–120°C [5]), R_f 0.80 (B). ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, Me), 4.35 s (2H, CH_2), 6.35 s (1H, CH), 6.53 s (2H, NH_2), 7.22–7.43 m (5H, Ph).

2-Amino-4-benzylthio-5-bromo-6-methylpyrimidine (IIb). A mixture of 0.4 g of free base **IIa** and 0.3 g of *N*-bromosuccinimide [19] in 15 mL of tetrachloromethane was refluxed for 1 h. The formed slurry was cooled to room temperature and allowed to stay overnight. The precipitate was filtered off, crystallized from 65% ethanol, and dried to a constant mass. Yield 0.125 g (24%), mp 141°C (mp 135–137°C [5]), R_f 0.51 (C). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, Me), 4.34 s (2H, CH_2), 6.76 s (2H, NH_2), 7.22–7.46 m (5H, Ph).

2-Amino-4-benzyloxy-6-methylpyrimidine (IId). A mixture of 1.5 g of isocytosine **IV**, 1.52 g of benzyl chloride, and 0.83 of calcined potassium carbonate in 25 mL of anhydrous DMF was kept at 80°C for 4 h. After cooling to room temperature the precipitate was filtered off, the filtrate was evaporated in a vacuum to dryness. The residue was ground with 5% solution of sodium hydroxide, the insoluble part was filtered off, thoroughly washed with water, and dried to a constant mass to obtain a mixture of compound **IId** and *N*-benzylisocytosine **XVII**, which was separated by treatment with 10 mL of acetonitrile with subsequent filtering off an insignificant insoluble residue. The precipitate separated from the solution after staying was filtered off, washed with a minimal amount of acetonitrile, and dried to a constant mass. From the filtrate, acetonitrile was removed, the residue was treated with benzene, the insoluble part was filtered

off, benzene was removed in a vacuum. The residue was crystallized from cyclohexane and dried to constant mass. Yield 0.17 g, mp 107°C (mp 108–109.5°C [14], 110–112°C [15]), R_f 0.61 (D). ^{1}H NMR spectrum, δ, ppm: 2.16 s (3H, Me), 5.29 s (2H, CH_2), 5.83 s (1H, CH), 6.34 s (2H, NH_2), 7.28–7.40 m (5H, Ph).

2-Amino-4-chloro-6-methylpyrimidine (III). A mixture of 6 g of isocytosine **IV** and 35 mL of freshly distilled phosphorus oxychloride was refluxed till the mixture became homogeneous, then the excess of the chlorinating agent was removed in a vacuum. For cooling, the residue was mixed with ice and treated with 25% aqueous ammonia to pH 8. The formed suspension was filtered, the precipitate was washed with water, crystallized from 50% ethanol, and dried to a constant mass. Yield 3.7 g (54%), mp 188°C (mp 182–183°C [7]), R_f 0.79 (D). Found, %: C 41.74; H 4.05; N 29.35. $C_5H_6ClN_3$. Calculated, %: C 41.83; H 4.21; N 29.27.

2-Amino-6-methylpyrimidin-4(3*H*)-thione (V). A mixture of 2.02 g of isothiouronium salt **VII** and 10% solution of potassium hydroxide prepared from 7 g of KOH was refluxed to homogeneous state. The reaction mixture was filtered from small impurities and evaporated to dryness in a vacuum. The residue was dispersed in 20 mL of water and treated with acetic acid to pH 6–7. The precipitate was filtered off, washed with water, and dried to a constant mass to give 0.98 g (85%) of isothiocytosine **V** with mp >250°C (decomp.) (mp 321°C [5], >190°C (decomp.) [9]), R_f 0.43 (B), which was used in S-benzylation without additional purification. Analytically pure sample of compound **V** was obtained by crystallization from 30% acetic acid with subsequent thorough washing with water and drying at 70°C for 10 h, mp >250°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.06 s (3H, Me), 6.31 s (1H, CH), 6.76 s (2H, NH_2), 11.91 br.s (1H, NH). Found, %: C 42.34; H 5.08; N 29.67. $C_5H_7N_3S$. Calculated, %: C 42.53; H 5.00; N 29.76.

(2-Formylamino-6-methylpyrimidin-4-yl)isothiouronium chloride (VII). A mixture of 2.3 g of pyrimidine **VI** and 1.02 g of thiourea in 25 mL of ethanol was refluxed for 3 h. After cooling the formed precipitate was filtered off, washed with ethanol, and dried to a constant mass to give 2.02 g (61%) of isothiouronium salt **VII**, mp 237°C (decomp.), R_f 0.43 (B), which was used in the preparation of isothiocytosine **V** without further purification. Analytically pure sample of compound **VII** was prepared by crystallization from the mixture of ethanol and DMF (1 : 4) with subsequent thorough washing with anhydrous diethyl ether and drying to a constant mass, mp 240°C (decomp.). IR spectrum, ν, cm^{-1}: 3081 m (C^5H), 2652, 2603, 2359, 2344 m (NH_2^+, NH^+), 1664 s (C=O), 1549 s (NH). Found, %: C 33.37; H 4.17; N 27.86. $C_7H_9N_5OS{\cdot}HCl$. Calculated, %: C 33.94; H 4.07; N 28.27.

6-Methylpyrimidin-4(3*H*)-one picrate (XI). To a 3–4% solution of hydrogen peroxide (50 mL) heated to 70°C 6 g of thiouracil **IX** was added by portions in the course of 30 min with vigorous stirring. After the addition was completed, the reaction mixture was kept at this temperature for 15 min, then cooled and neutralized with 10% aqueous solution of sodium hydroxide. The obtained solution was heated to 70°C and treated with 9.7 g of picric acid. The mixture was stirred at 90°C for 15 min to homogeneous state. After cooling to room temperature the formed suspension was kept for no less than 5 h, then filtered. The obtained precipitate was twice crystallized from water and dried to a constant mass. Yield 7.3 g (51%), mp 147°C, R_f 0.81 (A). Found, %: C 38.47; H 2.69; N 20.12. $C_5H_6N_2O{\cdot}C_6H_3N_3O_7$. Calculated, %: C 38.95; H 2.67; N 20.65.

4-Chloro-6-methylpyrimidine (XII). A mixture of 7.3 g of picrate **XI**, 100 mL of diluted (1 : 1) hydrochloric acid, and 50 mL of benzene was refluxed with vigorous stirring for 15 min. After cooling to room temperature the aqueous layer was separated, filtered from small amount of precipitated picric acid, and evaporated to dryness in a vacuum. The residue was refluxed with 50 mL of anhydrous acetonitrile, the insoluble part filtered from hot solution, washed with acetonitrile, and dried to a constant mass. Yield 2.54 g (80%), mp 222°C, R_f 0.65 (A). ^{1}H NMR spectrum, δ, ppm: 2.81 s (3H, Me), 6.88 s (1H, C^5H), 9.48 s (1H, C^2H), 9.74 br.s (2H, NH, N^+H). Found, %: C 40.54; H 4.60; N 18.92. $C_5H_7N_2O{\cdot}HCl$. Calculated, %: C 40.97; H 4.81; N 19.11.

4-Methyl-6-chloropyrimidine (XIII) was prepared similarly to compound **III** from 5 g of hydrochloride **XII** and 25 mL of freshly distilled phosphorus oxychloride. After treatment of the reaction mixture with 25% aqueous ammonia to pH 8 the product was extracted with dichloromethane (2 × 20 mL), the

organic layer dried over calcium chloride for 10 h, dichloromethane was removed, the residue was distilled in a vacuum collecting the fraction with mp 97–100°C (20 mmHg). Yield 3.29 g (75%), mp 35°C (mp 38–39°C [7], 34.5–36°C [10]), R_f 0.69 (C).

2-Benzylamino-4-benzyloxy-6-methylpyrimidine picrate (XV). *a*. To a solution of 0.24 g of sodium in 30 mL of anhydrous benzyl alcohol heated to 60°C 0.5 g of aminochloropyrimidine **III** was added. The mixture was stirred for 4 h. After cooling to room temperature the precipitate was filtered off, the filtrate was evaporated to dryness in a vacuum. To the residue 10 mL of ethanol was added and concentrated to the consistency of thick oil. The oil was extracted with benzene and filtered from small amount of impurities. To the filtrate the solution of 0.79 g of picric acid dissolved in 5 mL of benzene was added, the mixture was refluxed for 15 min, cooled to room temperature, the precipitate was filtered off, washed with benzene, and dried. After crystallization from a mixture of ethanol and DMF (4 : 1) the product was washed with ethanol and dried to a constant mass. Yield 0.24 g (15% to aminochloropyrimidine **III**), mp 176°C, R_f 0.89 (A). IR spectrum, ν, cm^{-1}: 607, 703, 738, 787, 815, 911, 924, 941, 984, 1000, 1027, 1081, 1163, 1174, 1262, 1317, 1334, 1357, 1428, 1437, 1474, 1497, 1510, 1548, 1568, 1630, 1654, 2976, 3096, 3228, 3306, 3447. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H, Me), 4.67 d (2H, $\underline{CH_2}$NH, *J* 5.3 Hz), 5.43 s (2H, CH_2), 6.36 s (1H, CH), 7.33 s (10H, Ph), 8.56 s (2H, Ph), 8.62 br.s (1H, NH). Found, %: C 55.78; H 4.10; N 15.83. $C_{19}H_{19}N_3O{\cdot}C_6H_3N_3O_7$. Calculated, %: C 56.18; H 4.15; N 15.72.

b. To a solution of 0.18 g of sodium in 15 mL of anhydrous benzyl alcohol heated to 60°C 0.6 g of benzylaminochloropyrimidine **XVI** was added. The mixture was stirred at 140°C for 4 h, cooled to room temperature, the precipitate filtered off, the filtrate was evaporated to dryness in a vacuum. The residue was dissolved in 15 mL of benzene, the solution was filtered from small impurities and decanted from a small amount of tick oily substance. To the solution, 0.85 g of picric acid was added and the obtained mixture was refluxed for 15 min. After cooling to room temperature the precipitate was filtered off, washed with benzene, and dried. After crystallization from a mixture of ethanol and DMF (4 : 1) the product was washed with ethanol and dried to a constant mass. Yield 0.68 g (50% to benzylaminochloropyrimidine **XVI**).

2-Amino-3-benzyl-6-methylpyrimidin-4(3*H*)-one (XVII). The precipitate separated from the acetonitrile solution (see the synthesis of compound **IId**) was crystallized from 40% ethanol and dried to a constant mass. Yield 63 mg, mp 211°C, R_f 0.43 (D). IR spectrum, ν, cm^{-1}: 1688, 1681 s (C=O), 1649, 1644 s (NH_2). ^{1}H NMR spectrum, δ, ppm: 2.04 s (3H, Me), 5.11 s (2H, CH_2), 5.53 s (1H, CH), 6.97 s (2H, NH_2), 7.19–7.29 m (5H, Ph). Found, %: C 66.61; H 5.89; N 19.46. $C_{12}H_{13}N_3O$. Calculated, %: C 66.96; H 6.09; N 19.52.

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REFERENCES

1. Liu, X. and Xu, L., *Shandong Yike Daxue Xuebao*, 1993, vol. 31, no. 2, p. 176; *C. A.*, 1994, vol. 120, 54509n.
2. Liu, X.Y. and Xu, L.J., *Yaoxue Xuebao*, 1994, vol. 29, no. 2, p. 153; *C. A.*, 1994, vol. 121, 108682e.
3. Orzeszko, B., Laudi, A.E., Starosciak, B.J., Orzeszko, A., and Kazimierczuk, Z., *Acta Polon. Pharm.*, 2004, vol. 61, no. 6, p. 455.
4. Feldman, I.Kh. and Kheifits, G.M., *Zh. Obshch. Khim.*, 1961, vol. 31, no. 3, p. 755.
5. Koppel, H.C., Springer, R.H., Robins, R.K., and Cheng, C.C., *J. Org. Chem.*, 1961, vol. 26, no. 3, p. 792. DOI: 10.1021/jo01062a037.
6. Erkin, A.V. and Krutikov, V.I., *Russ. J. Gen. Chem* ., 2012, vol. 82, no. 9, p. 1567. DOI: 10.1134/S1070363212090198.
7. Gabriel, S. and Colman, J., *Ber*., 1899, vol. 32, no. 3, p. 2921. DOI: 10.1002/cber18990320352.
8. Polonovski, M. and Schmitt, H., *Bull. Soc. chim. France*, 1950, nos. 7–8, p. 616.
9. Felczak, K., Bretner, M., Kulikowski, T., and Shugar, D., *Nucleosides & Nucleotides*, 1993, vol. 12, no. 2, p. 245. DOI: 10.1080/07328319308021210.
10. Marshall, J.R. and Walker, J., *J. Chem. Soc*., 1951, no. 4, p. 1004.
11. *Organic Syntheses*, Moscow: Inostrannaya Literatura, 1956, vol. 7, p. 39.
12. Erkin, A.V., Krutikov, V.I., and Smirnova, E.B., *Russ. J. Gen. Chem* ., 2008, vol. 78, no. 10, p. 1944. DOI:

10.1134/S1070363208100216.

13. Sprinzak, Y., *J. Am. Chem. Soc*., 1956, vol. 78, no. 13, p. 3207. DOI: 10.1021/ja01594a064.
14. Bolhofer, W.A., USA Patent 4144338, 1979; *C. A*., 1979, vol. 91, p. 20548s.
15. Chun-Ho Wong, Wing-Shong Chan, Chui-Man Lo, Hak-Fun Chow, To Ngai, Ka-Wai Wong, *Macromolecules*, 2010, vol. 43, no. 20, p. 8389. DOI: 10.1021/ma101647j.
16. Sheldrick, G.M., *Acta Crystallogr. A,* 2008, vol. 64, no. 1, p. 112. DOI: 10.1107/S0108767307043930.
17. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K., and Puschmann, H., *J. Appl. Crystallogr*., 2009, vol. 42, no. 2, p. 339. DOI: 10.1107/S0021889808042726.
18. CrysAlisPro, *Agilent Technologies*, Ver. 1.171.36.20 (release 27-06-2012).
19. *Weygand-Hilgetag. Organisch-Chemische Experimentierkunst*, Moscow: Khimiya, 1968, p. 137.